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Applications of Silicon Compounds in the Synthesis of Insect Pheromone Analogs.

Oanh Thi vu Nguyen

Louisiana State University and Agricultural & Mechanical College

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**Applications of silicon compounds in the synthesis of insect
pheromone analogs**

Nguyen, Oanh Thi Vu, Ph.D.

The Louisiana State University and Agricultural and Mechanical Col., 1987

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APPLICATIONS OF SILICON COMPOUNDS
IN THE SYNTHESIS OF INSECT PHEROMONE ANALOGS

A Dissertation

Submitted to The Graduate Faculty of The
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Danh Thi Vu Nguyen
B.A., New England College, 1978
August, 1987

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OANH THI VU NGUYEN

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Delicated with love to my late parents,
my sister Nhan, my brothers Tan and Rung
my husband Binh, and my niece HaQuyen.

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ABSTRACT

Pheromones are highly active chemical messengers which are secreted by a member of an animal species and elicit a definite behavior in other members of the same species. The study of insect pheromones has recently attracted great attention because of their purely scientific interest and their favorable prospects for the control of pest insects. The study in this dissertation aims at the elucidation of some important aspects of the mechanism of perception of insect pheromones, which is based on the fact that the cyclic analogs of the natural pheromone have partially fixed conformations, whereas the straight-chain natural pheromone is more flexible and can adopt numerous conformations. The cyclic compound which best mimics the action of the natural pheromones presumably has a conformation similar to that which the pheromone adopts when bound to the receptor site. The project includes the following:

1. Syntheses of cyclic analogs of natural pheromones:
 - (i) 4-ethyl-3-(5-acetoxypentyl)cyclopentene [20] and its cyclopentane [18].
 - (ii) 4-methyl-3-(5-acetoxypentyl)cyclohexene [21] and its cyclohexane [19].
2. Structure elucidation including conformational

analysis.

3. Results of conformational energies derived from MM2 calculations.

Compound [20] was synthesized from the kinetic silyl enol ether of 2-(5-acetoxypentyl)-3-ethylcyclopentanone [37] which was treated with $\text{BH}_3\cdot\text{THF}$, followed by acidification, to give [20]. Compound [21] was also obtained using the same method from 2-(5-acetoxypentyl)-3-methylcyclohexanone [63]. Compound [37] was reacted with p-toluenesulfonylhydrazine in DMF-sulfolane having p-toluenesulfonic acid monohydrate as catalyst, followed by NaBH_3CN to give 2-(5-acetoxypentyl)ethylcyclopentane [18]. In a similar manner, 2-(5-acetoxypentyl)methylcyclohexane [19] was obtained from [63]. Several less successful routes to these disubstituted ring compounds were explored.

The structures of [18 - 20] were assigned based on ^1H NMR, ^{13}C -NMR, IR, and MS spectral data. Their stereochemical assignments have been made on the stereochemistry of analogs, their epimerization under alkaline conditions, or the coupling constants of the two hydrogen atoms on the two carbons bearing substituents. The most stable conformations of the 5- and 6-membered ring systems are in an envelope and a chair forms, respectively from MM2 calculations.

CHAPTER I: INTRODUCTION

I. INTRODUCTION:

During the past 20 years there has been a rapid expansion in the chemical identification and synthesis of insect pheromones,¹ at least partially in an effort to provide alternatives to the use of insecticides for the control of insect populations. The identification of a pheromone and the development of a practical chemical synthesis allow the necessary biological research to be carried out to determine whether or not the compounds can be used to interfere with the normal behavior of the insect species and to aid in successful pest control. Pheromones are highly active chemical messengers which are secreted by a member of an animal species and elicit a definite behavior in other members of the same species. Various insect behaviours are also controlled by pheromones. Pheromone compounds are used in intraspecific communication to regulate the behavior of animals (insects in particular) in such activities as attraction to the opposite sex, aggregation of both sexes, sexual stimulation, and trail following. These responses are brought about by remarkably low concentrations of the pheromone component. Pheromones constitute only one category under the general term "semiochemicals" (semeion=signal), which include both inter- and intraspecific signals.

Studies of insect pheromones have recently attracted great attention because of their purely scientific interest and their favorable prospects for the control of pest insects.² Though no pheromone has to date been fully registered for use in crop protection,³ progress has been made in the application of several pheromones in pest control programs and some experimental use permits have been granted by the U.S. Environmental Protection Agency. Survey and monitoring traps incorporating synthetic sex pheromones have been widely used for measuring the presence and abundance of pest populations and are commercially available. Many different experiments at insect control have also been carried out with varying success using mass trapping, host baiting, and communication disruption techniques.⁴

There are more than a million species of insects in nature. Among this wide variety similar species are encountered, which are almost indistinguishable in their external features. However, in the world of insects there is almost never any crossing of different species. The maintenance of "order" in nature is favored by a number of refined phenomena involving sight, hearing, and especially smell, which is very highly developed in insects. This enables them to find food, sites for the deposition of eggs, and also individuals of the opposite sex.

The French naturalist Jean Henri Fabre was the first to note at the end of the XIXth century that the female of *Saturnia peri* (L) placed in a cage attracted a large number males. He carried out experiments with other species of butterflies (moths) and concluded that the female executes vibrations which are propagated in air in the form of waves and are received by the antenna of the male. Later it was established that the information provided by the female is transmitted with the aid of a chemical substance. These substances have been called sex attractants (the compounds secreted by one insect in order to influence another individual of the same species and to induce in the latter definite responses) are frequently called pheromones as indicated above.³ Kirshenblat proposed a classification of such compounds and introduced the term "telergones".⁴

Although observations that male moths are attracted over considerable distances to females of the same species have been made during the last century, it was not until 1959 that an active compound from a female moth was chemically identified by Butenandt et al.⁵. Karlson and Luscher coined the term pheromone for such intraspecific chemical signals.⁶

Butenandt's achievement - the identification of bombyko [1], a single, active compound from hundred of



[1]

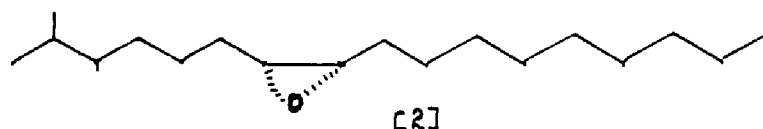
thousands of female silkworm moths (*Bombyx mori*) over a 25-year period without benefit of modern instrumentation—misled a number of subsequent investigators who uncritically adopted his bioassay, which involved short-range sexual excitation. This was the appropriate response to measure in an insect that had been domesticated for silk production and no longer occurred in field populations, but it was later misused in monitoring chemical fractionation in the search for long-range attractants.

Furthermore, investigators of female moth pheromones through the 1960's searched for the single unique compound that would elicit a particular response. In most instances, the compound isolated through laboratory bioassays did not effectively attract male moths in field populations. In 1969, Moorhouse et al.⁷ reported that the male red ballworm (*Diparopsis castanea*) responded in a laboratory bioassay to five substances isolated from the female, and that three fractions separated by gas chromatography (GC) produced an electroantennogram (EAG) response from male antennae. They suggested that failure to obtain a good field

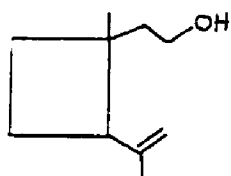
response for several species of moths was a consequence of failure to identify other active components of the pheromone: they proposed EAG recording of GC fractions, which has also been extensively exploited by Roelofs.¹⁰ As early as 1964, Wright¹¹ suggested that multicomponent pheromones would be expected to convey more information than single compounds and that such multicomponent communication systems would have evolved in nature. During 1970's, most of the moth pheromones described were multicomponent, and reinvestigation of those identified earlier usually resulted in the identification of additional components, with a conspicuous improvement in the field responses. The "missing" component in several cases was found to be a small amount of the geometric isomer of the unsaturated component originally identified.

Typically, but with some exceptions, moth pheromone components are longchain, unsaturated acetals, alcohols, and aldehydes. The pheromone may be a mixture of positional isomers, or structurally similar nonisomers. In a number of cases, a precise ratio of geometric isomers determines which of several closely related species is attracted in the field. An occasional epoxide, ketone, or hydrocarbon has been reported. Several moths respond to a single compound; the sex attractants of the gypsy moth, *Lymantria dispar*, for example, is a chiral

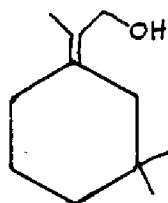
molecule, and the moth responds only to the (7R,8S)-(+)-cis-7,8-epoxy-2-methyloctadecane enantiomers [2]



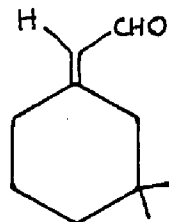
The male cotton boll weevil, *Anthonomus grandis*, produces a four-component [3-6] synergistic pheromone, which aggregates males and females in the field.¹²



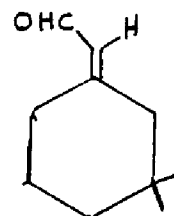
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[4]

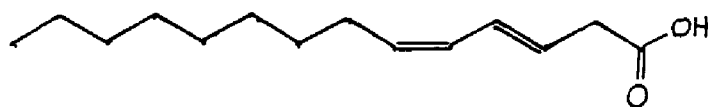


[5]



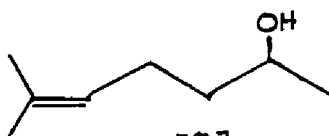
[6]

Not all beetles use multicomponent pheromones. The sex excitant and attractant pheromone emitted by the female black carpet beetle, *Attagenus megatoma*, apparently consists of a single compound, megatomoic acid [7].¹³



[7]

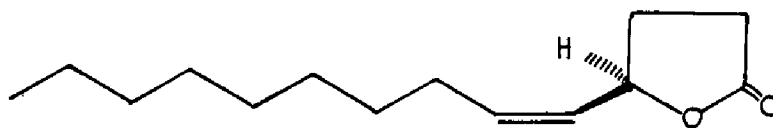
An ambrosia beetle in the Pacific Northwest (*Gnathotrichus sulcatus*) degrades logs and lumber by boring directly into the xylem. In this process the male releases sulcatol [8], which aggregates both sexes. However,



[8]

neither enantiomer of [8] is attractive by itself; rather, a synergistic mixture of both enantiomers (over a rather broad range of ratios) is required. A closely related, sympatric species, *Gnathotrichus retusus*, produces and responds to only a single enantiomer of the same compound; the response is inhibited by the other enantiomer. They thus furnish an example of enantiomer-based interruption of attraction between sympatric species.¹⁴

The pheromone of the Japanese beetle, *Popillia japonica*, consists of a single enantiomer, japonilure [9], and the addition of even a few percent of the antipode diminishes the response.¹⁵



[9]

In the case of the insects mentioned above that produce chiral compounds, the response is to only one of the enantiomers. The other isomer appears to be inert and does not interfere. Interpopulational differences and interspecific interactions have been demonstrated at the level of enantiomers.^{14, 15}

These few examples of pheromones provide evidence of the diversity, complexity, sensitivity, and specificity of such behavioral chemicals.¹⁷ One further problem in studying them is that the extract of a pheromone-emitting gland may not represent the actual airborne message perceived by the recipient, in which case collection of the airborne material may be the best procedure.¹⁸

Several recent reviews discuss the practical applications of pheromones,¹⁹ which can be categorized as follows:

1. Pheromones used in trapping insects for monitoring and survey. Insect populations can thus be estimated and new areas of infestation can be detected at a very early stage. Such applications of pheromones allow the use of

insecticides only when needed.

2. Pheromones used as lures in circumscribed areas that are treated with insecticides, hormone analog, or pathogens. Insects lured to the areas become coated or infected with the harmful substances that they then spread to the rest of the population.

3. Pheromones used in the mass trapping of insects for population suppression.

4. Pheromones used to permeate the air to disrupt mate-finding or aggregation, the end result being population suppression. Parapheromones (chemicals that mimic pheromones) or antipheromones (chemicals that interrupt responses) may also be used.

The phenomenon of perception of simple, volatile chemicals on the insect antennae is one of major interest in itself, as well as representing one of the simplest manifestations of the very general biological device of specific molecule-receptor site interactions, a device adapted to a multitude of purposes in all living system. Since the insect pheromone system is one of the simplest of these devices in nature, there is a reasonable possibility that an understanding of the physiology associated with pheromone perception can be developed in some detail, and that understanding can suggest means of investigating receptor site functions in more complicated systems.

Two facets of the communication system which require elucidation are the mechanisms of perception at the antennal receptor sites and the conversion of those, presumably principally electrical, signals into a behavioral response on the part of the insect. The present research is designed to acquire information concerning the former function, already in itself a formidably complex process. Perception at antennal receptor sites is frequently discussed simply in terms of "fit" of a stimulant molecule at a receptor site, but clearly the process is more complex than that. Kaissling^{20,21} has described a sequence of events beginning with absorption on the sensillum (the antennal morphological feature, or olfactory hair, containing one or more sense cells), and concluding with inactivation of the stimulant molecule and its removal from the receptor. Thus, in addition to receptor "fit", rates of such processes as diffusion through a proteinaceous coating on the sensillum, penetration from an outer lipophilic phase to an inner hydrophilic one, enzymatic metabolism of the stimulant molecule, and probably other processes, influence the overall process of perception. Nevertheless, an integral part of the sequence of events is the binding on insect antennae, which generally requires on the part of the stimulant molecule one (and probably sometimes more) functional group and also a more or less specific

size and shape.

The simplest mechanism of pheromone perception is apparently that exemplified by the responses of the silkworm moth *Bombyx mori* (Linnaeus) to its sex pheromone, bombykol. Response to sex pheromone can in general be measured in three ways:

1. Behavioral response: including the insect's following a plume of pheromone in moving air, as well as the display of characteristic pre-copulatory behavior.
2. Antennal response in the form of an electroantennogram, measuring the total electrochemical potential generated by whatever receptor sites are being stimulated on the whole antenna.²²
3. Single olfactory cell response measured electrically using microelectrodes.²³

In the case of *B. mori* there are apparently receptors for bombykol which respond most strongly to bombykol itself and less strongly to molecules having even a minor structural variation from that of bombykol. Bombykol and its analogs are also not giving any appreciable stimulation to nonpheromone, or odor generalist, receptor sites on the antenna. These conclusions arise from the fact that bombykol and a series of analogs elicit the same relative responses regardless of which of the three means of measuring response is employed.²⁰ Results of this kind led to the conclusion that *B. mori* employs only a

single compound interacting at a single kind of receptor as its complete sex attractant that the female emits a second pheromone component which specifically stimulates a second kind of olfactory cell of the male moth.²⁴

Several complicated stimulus-response mechanisms operate in some insects. Sometimes the sex pheromone is a two-, or even a multicomponent mixture of compounds, which are usually chemically closely related. The redbanded leafroller, *Argyrotaenia velutinana* (Walker), employs Z- and E-11-tetradecenyl acetates, and male sexual attraction is strongly dependent on the ratio of geometric isomers.²⁵ Electrical responses of single olfactory receptor neurons of male *A. velutinana* have been elicited by the acetates above, as well as six other related, behaviorally active compounds.²⁶ Response frequencies to equal concentrations of each of the compounds, and also changes in response frequency with increasing amounts of any one compound, varied from receptor to receptor. It is concluded that there must be at least two, and probably more, functionally different kinds of receptor sites for each of the two olfactory neurons in each sensillum. In addition to the differences in quantitative responses, the range of compounds which elicit responses from *A. velutinana* neurons varies from one neuron to the next (in contrast to *B. mori*). Furthermore, a range of compounds may elicit strongly

excitatory responses. More recent work has demonstrated again that there are at least two receptors on redbanded leafroller antennae, and also that they exhibit stereospecificity in their binding of the separate enantiomers of a chiral pheromone analog.²⁷ Clearly the situation is much more complex with the redbanded leafroller than it is with the silkworm moth.

In a number of insect species it has become clear that there is an ability to distinguish a spectrum of odors on so-called odor generalists cells. A most interesting and classical study²⁸ is that of von Frisch on the conditioning of worker bees to respond specifically to several different unrelated compounds. More recent work²⁹ has defined at least ten separate cell types in the honey bee, which allow a wide range of odor discrimination. Clearly, if insects in general have a highly developed sense of olfaction, then the three measures of responses to pheromone referred to earlier may be looking at quite different processes. Specifically, the behavioral and/or the whole antennal response may be arising due to stimulation of several different kinds of receptor sites. Indeed, behavior may very well be the result of integration by the insect's nervous system of more than one cue. For instance, there may be a principal cue for stimulating sexual response which depends on activation of the specific pheromone-

sensing cells, but the response may be modified by other olfactory cues being received simultaneously. Indeed, behavioral response does depend on a variety of factors in addition to the presence of pheromone, and these include time of day, light intensity and age of insect.³⁰ Since secondary cues are important, it is not unreasonable to propose that some of the secondary cues may be olfactory. In some species investigations have revealed that there are synergists which are ineffective at eliciting a significant behavioral response themselves, but which give rise to an augmented response, measured behaviorally^{23,31} when presented to the insect along with pheromone. In some cases, the synergists are clearly not components of the natural pheromone.

One of the most thorough published studies of pheromone synergists (and inhibitors) is that of Roelofs and Comeau³² who found a number of synergists for the redbanded leafroller by baiting traps with Z-11-tetradecenyl acetate and congeners. It is unreasonable to suppose that all of the compounds found to be synergists in that study are produced in the female pheromone gland. With other species, minor components of the mixture of compounds in the sex gland give rise to enhanced response when mixed with the major pheromone component.³³ Whether these minor components should be called synergists, or whether the mixture of compounds

should be referred to as a multi-component pheromone system is perhaps a matter of semantics.

In addition to synergists, pheromone inhibitors also exist. In some cases it appears that the inhibitor is interacting with the same receptor that binds the pheromone^{32,34} and in other case different receptors are involved.³⁵ The mechanism of inhibition may involve one of the following:

1. preferential binding of the inhibitor at the pheromone receptor site and failure of bound inhibitor to give the appropriate electrophysiological response.

2. inhibitor is bound at least competitively with pheromone at the pheromone receptor site but inhibitor is not readily released, giving rise to rapid saturation of the receptor sites.

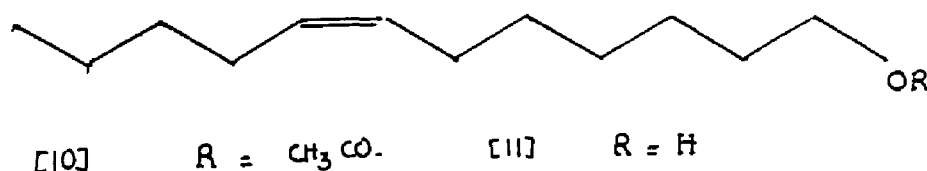
3. inhibitor is bound at a separate receptor site, and response it elicits overrides that of pheromone.

Understanding of the nature of the phenomenon of inhibition, synergism, and indeed of primary pheromone perception itself, is being handicapped by the fragmentary nature of much of the research in the area. It has finally become clear that the detailed mechanism of perception can vary from one insect species to another. Quite properly, much of the research up to this time has been aimed at characterization of the pheromonal compounds for a wide variety of insects. Observations

that would help define the chemistry and physiology of pheromone perception have been much less common. Much published research has used only one means of biological assay, most frequently either a behavioral one or an electroantennogram. Confusion has sometimes arisen due to the lack of correlation between response to a given stimulant when the response are measured in different ways. Indeed, only with *B. mori* a has fairly large body of work involving measurement of single cell responses at highly specific olfactory cells published. It is not clear whether the relatively simple mechanism operating in *B. mori* is a common one in insects, or whether the complexities of the *A. velutinana* system represent a more typical situation.

In our research group, we are interested in synthesizing the analogs of natural pheromones. The pheromone analogs have structures which vary from that of the natural pheromone in systematic ways to allow assessment of the conformation, as well as the electronic properties, of the receptor site. The compounds to be assayed are designed to afford information about the molecular conformation and functionality required to bind at the receptor site, as well as general characteristics such as polarity and lipophilicity. The study will concentrate on the cabbage looper, *Trichoplusia ni* (Huebner) which is an economically important pest in the local area as well

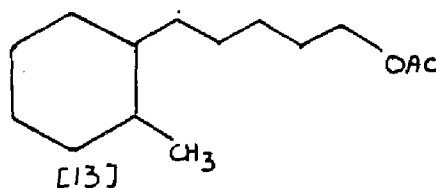
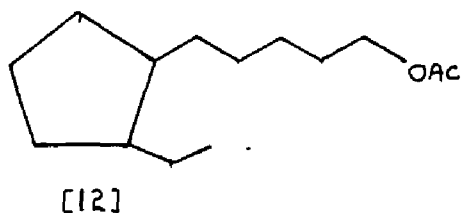
as nationwide. Additionally, this species has been chosen for concentration because it is a species with a well-characterized sex pheromone with one main component, Z-7-dodecenyl acetate [10], identified some time ago.³⁶

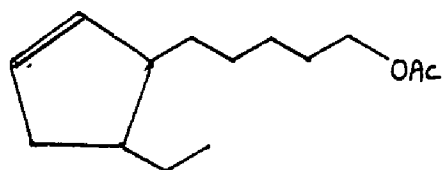


Adult male cabbage loopers respond well behaviorally to [10] alone^{36,40} and much less actively to a number of closely related compounds.^{37,41} The alcohol corresponding to the acetate, Z-7-dodecen-1-ol [11], has been characterized as an inhibitor,^{35b} in that it prevents male moths of *T. ni* from orienting to a locus of evaporating [10]. However, perception of [10] is not blocked by [11], since males still show excited upwind flight when exposed to [10+11], and pre-exposure to [11] does not cause fatigue of the male response to [10]. The morphology of the *T. ni* antennae has been described in some detail,⁴² and there are several kinds of sensory sensilla. By far the most numerous are the sensilla trichodea, which are assumed to be the principal olfactory sensors. Of the 3 to 4 neurons associated with a sensillum trichodeum, it is reported that one responds

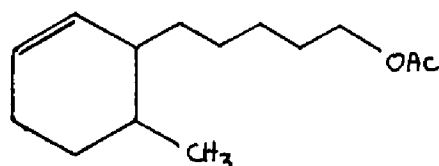
electrophysiologically to [10] and another responds to [11], with no apparent peripheral interaction.^{43,44} Thus, there appears to be in *T. ni* a highly specific pheromone receptor, the response of which to pheromone analogs can be measured in a single cell experiment. Interestingly, in an electroantennogram experiment, no difference could be discerned between [10] and [11].⁴⁵ Again, the point should be emphasized that single measures of responsiveness are inadequate to characterize the pheromone system. Indeed, even in measurements of single cell responses, more than one parameter may be measured. The amplitude of the saturated cell response does not show the same dependence on molecular structure of the stimulating odor as the half-time for decline of the potential shows.⁴⁶

The research in this dissertation will focus on the synthesis of the cyclic analogs [12-15] of the principal constituent of the cabbage looper sex attractant pheromone [10]. Cyclic analogs of the natural pheromone will have partially fixed conformations, whereas the straight-chain natural pheromone is more flexible and can adopt





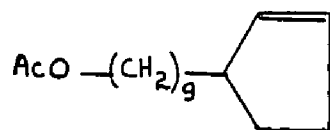
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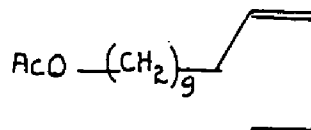
[15]

numerous conformations. The cyclic compound which best mimics the action of the natural pheromone presumable has a conformation similar to that which the pheromone adopts when bound to the receptor site. It has been reported⁴⁷ that males of *Ostrinia nubilalis* (Huebner), the European corn borer, respond in precopulatory behavior to the unsaturated cyclic pheromone analog [16], as well as they do to the pheromone [17]. There have not been reports of the testing of cyclic analog such as [13-15].

In addition to the synthetic work, conformational energies of partial structures of [13-15] were calculated using force field (MM2) in order to define as clearly as possible the stereochemical differences between the acyclic pheromone itself and the cyclic analogs.



[16]



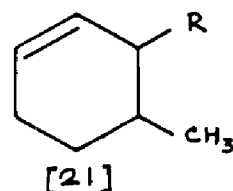
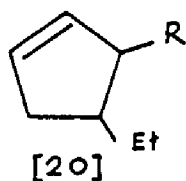
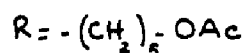
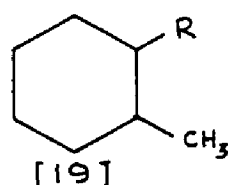
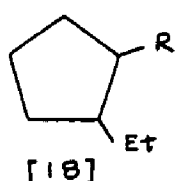
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CHAPTER II: RESULT AND DISCUSSION.

I. OUTLINE OF RESULT AND DISCUSSION OF 5-MEMBERED RING:

1. Introduction:

As previously mentioned, pheromonal studies in this dissertation involve the preparation of cyclic analogs of natural pheromones such as [18-21]:

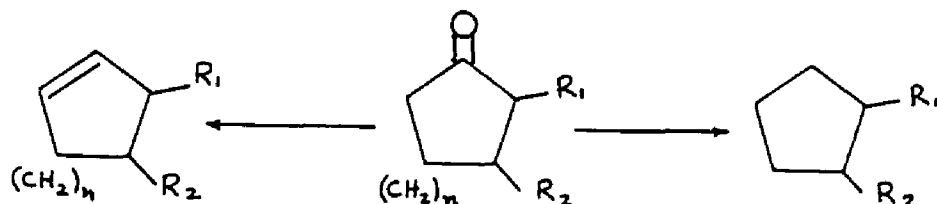


The synthetic pathways involve suitably functionalized five- and six-membered rings; namely, α, β -dialkylcyclopentanones and α, β -dialkylcyclohexanones. Later conversion of five- and six-membered rings; namely, α, β -dialkylcyclopentanones and α, β -dialkylcyclohexanones. Later conversion have been utilized. This introduction section will review methods to make α, β -dialkylcyclopentanones, the key intermediate in this chapter. The preparation of α, β -dialkylcyclohexanones will be considered later. The general process is shown in Scheme 1.

Since silyl enol ethers will play an important role in

the conversion of the ketone functional group in the α, β dialkylcycloalkanones (Scheme 1) to the alkene, and will be used in many of the schemes to be described, their applications in organic syntheses are also cited here.

Scheme 1.



$R_1 = -(\text{CH}_2)_5-\text{OAc}$; $R_2 = \text{Et}$ for $n=1$; $R_2 = \text{Me}$ for $n=2$

2. Application of silyl enol ethers in synthesis:

Trimethylsilyl enol ethers have become extremely important intermediates in synthetic chemistry for the regiospecific generation of enolates to be used in directed aldol condensations, the production of α -substituted carbonyl derivatives, the preparation of cyclic alkenes via hydroboration-elimination, and in many thermal and photochemical cycloaddition reactions.^{4a}

Silyl enol ethers are very useful for the preparation of α -substituted carbonyl compounds, and they have found a number of other uses in organic synthesis as well. Their first applications in synthesis were as precursors to enolate anions, intermediates of enormous importance in organic chemistry. Treatment of trimethylsilyl enol

ethers with MeLi generates lithium enolates, and the by-product Me₄Si is volatile and unreactive. Enolates have also been generated by treating silyl enol ethers with other nucleophiles, including fluoride ion.⁴⁹

Specific metal enolates are not always alkylated regioselectively, nor is there always complete control over the degree of alkylation. These difficulties can sometimes be overcome using enol derivatives, of which silyl enol ethers are particularly effective. A direct alkylation of an enolate formed by a conjugate addition may not be ideal. If the enolate is trapped and purified as the silyl enol ether, it can be regenerated in a different medium to undergo a regioselective alkylation.

Silyl enol ethers have more recently been found to react directly with a wide variety of electrophilic reagents, yielding a variety of α -substituted carbonyl compounds. In most cases studied, these reactions have been found to be regiospecific.

Cyclic enol ethers readily undergo hydroboration-elimination upon treatment of the intermediate organoborane with an acidic catalyst to provide cyclic alkenes.⁴⁹

Silyl enol ethers of ketones are commonly prepared from enolate anions by treatment with silylating agents such as Me₃SiCl. Silyl enol ethers of esters and amides may sometimes be prepared by silylation of the enolates; however, in some cases silylation takes place at carbon,

depending on substrate, silylating agent, and reaction conditions.⁴⁹

Trimethylsilyl enol ethers are also commonly prepared from ketones and aldehydes by treatment with Me_3SiCl and Et_3N in DMF (or $\text{Me}_3\text{SiCl}/\text{Et}_3\text{N}/\text{ZnCl}_2$). This procedure gives predominantly the more stable isomer from an unsymmetrical ketone. "Kinetic" silyl enol ethers are very selectively formed from ketones by using first lithium diisopropylamide (LDA) to generate the lithium enolate and then O-silylating with Me_3SiCl .

3. Review of the preparation of α, β -dialkylcyclopentanones:

a. General strategy:

Normally, cyclopentanones are difficult to alkylate specifically at the α -position because of the relative ease of enolization, aldol condensation,⁵⁰ O-alkylation in place of C-alkylation, and polyalkylation, as well as the fact that a specific enolate may not be alkylated regiospecifically.⁵¹ Because of these problems the alkylation of cyclopentanones is rarely done by the most obvious method: treating the carbonyl compound with base and an alkyl halide.⁵² The traditional solution to this problem is to use β -dicarbonyl compounds, which are less apt to give polyalkylation, and which alkylate specifically between the two carbonyl groups. More recently, Stork, having found enamines a useful but limited alternative to

enolates, discovered that lithium enolates are much better behaved than sodium or potassium enolates.²² Lithium enolates (but not sodium or potassium enolates) can engage in reactions with carbon electrophiles without loss of regiospecificity. Either sodium or potassium enolates lead to some polyalkylated material, whereas lithium gives more monoalkylation.

Although the general routes for the alkylation of cyclopentanones at the α -position via lithium enolates are known, it is much less straightforward to introduce an additional alkyl at the β -position. 2-Cyclopentenones, 2-alkyl-2-cyclopentenones, and 2,3-dialkyl-2-cyclopentenones are suitable starting materials for synthesis of α, β -dialkylcyclopentanones. They are converted to the α, β -dialkylcyclopentanones by conjugate addition-alkylation, conjugate addition, and reduction of the $-C=C-$ bond, respectively. An advantage of these conversions is stereochemical control at C-2 and C-3 due to the stereospecificity of the reactions in providing predominantly more of the stable trans isomer, which is the natural configuration seen in 11-deoxyprostaglandins, for instance.

b. Classification of synthesis:

α, β -Dialkylcyclopentanone syntheses may be divided into three major classes: i. synthesis in which 2-cyclopentenones are the precursors. ii. synthesis which

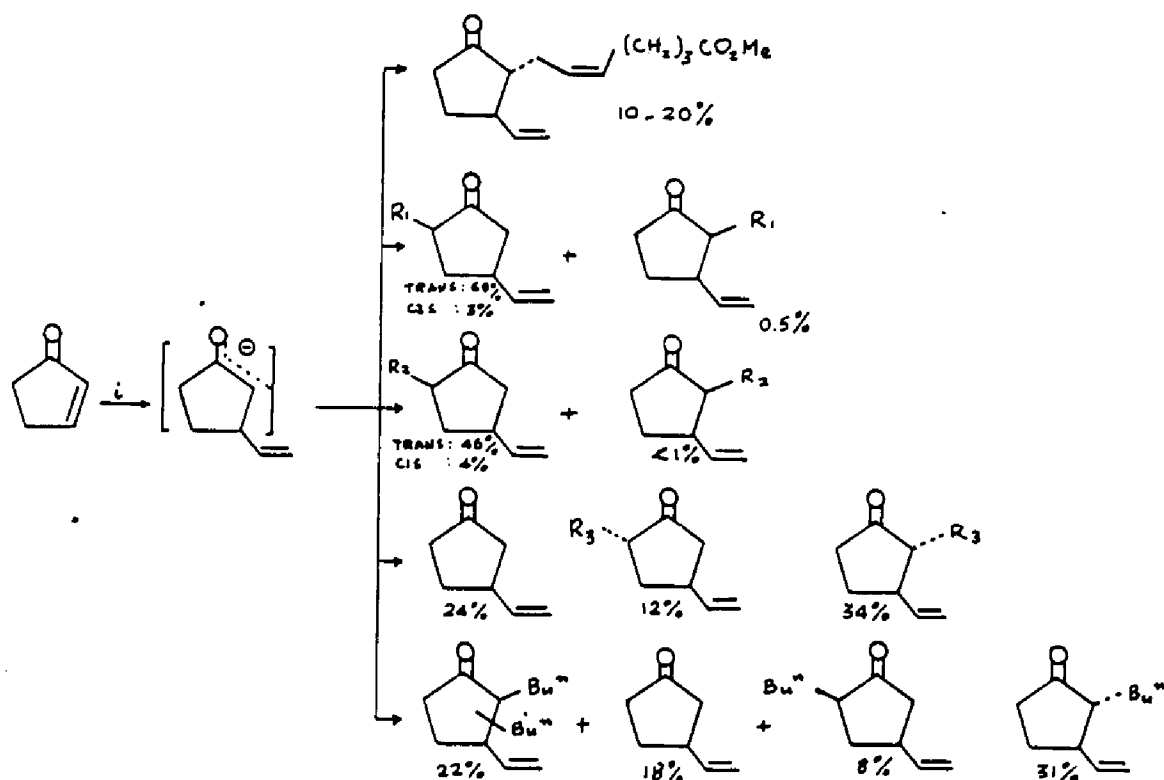
commences from 2-alkyl-2-cyclopentenones. iii. synthesis in which 2,3-dialkyl-2-cyclopentenone is used as the starting material. The discussion below will follow this classification.

4. 2-Cyclopentenone precursors: conjugate addition-alkylation approaches.

In 1975, Posner²⁴ and his co-workers succeeded in converting 2-cyclopentenone directly into 2,3-dialkylcyclopentanones by developing a nucleophilic β -alkylation and electrophilic α -alkylation procedure in one pot (Scheme 2). However, the one-pot reactions from Posner's methodology are only been partly successful due to lack of reactivity of the resultant enolates toward alkyl halides.

²⁵ In order to accomplish the reaction, several devices have been used: i. conversion of the resultant copper lithium enolate to the lithium enolate.²⁶ ii. direct α -alkylation of the lithium enolate resulting from the Michael addition of a lithium salt of the protected cyanohydrin²⁷ (e.g. $R-CH=CH-C(CN)(Li)-O-CH(CH_3)-O-Et$ to cyclopent-2-enone. iii. use of formaldehyde as an enolate ion trapping agent²⁸ iv. the direct enolate ion trapping method with acyl halide instead of alkyl halides.²⁹ In 1976, Toru³⁰ and his co-workers reported the successful trapping of the enolate ion by chlorocarbonate ester and subsequent alkylation to make prostaglandin analogues (α, β -dialkylcyclopentanones)

Scheme 2.



i. $\text{Me}(\text{CH}_2=\text{CH})\text{CuLi}$, -78°C ;

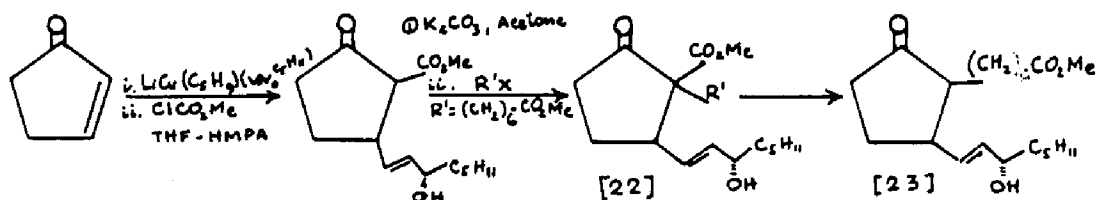
ii. RX where $\text{X} = \text{Cl}, \text{Br}, \text{I}$ and $\text{R} = \text{R}_1, \text{R}_2, \text{R}_3$.

$\text{R}_1 = -\text{CH}_2-\text{CH}=\text{CH}_2$. $\text{R}_2 = -\text{CH}_2-\text{CO}_2\text{Et}$.

$\text{R}_3 = -\text{CH}_2-\text{CH}=\text{CH}-\text{Me}$.

(Scheme 3). There was no report on stereoisomer ratios of [22] or [23] as obtained by Toru.

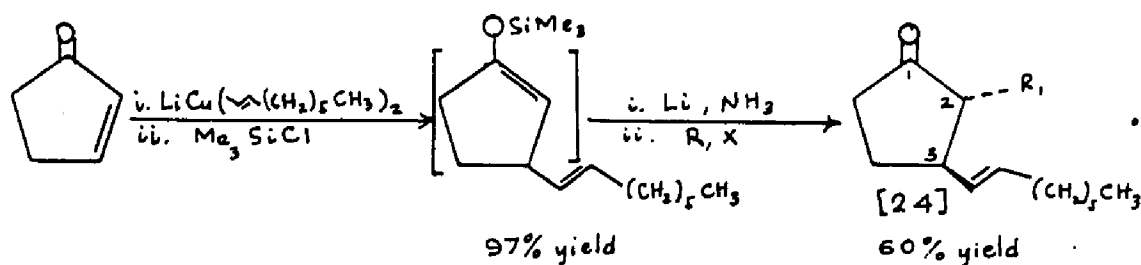
Scheme 3.



- i. $\text{LiCu}[\text{C}_5\text{H}_9][\text{CH}_2-\text{CH}=\text{CH}-\text{CH}(\text{OH})(\text{C}_5\text{H}_{11})]$
 ii. ClCO_2Me , THF-HMPA. iii. K_2CO_3 , Acetone.
 iv. $\text{X}-(\text{CH}_2)_6-\text{CO}_2\text{Me}$. v. H_3O^+ .

Patterson and Fried²⁶ have used Me_3SiCl to trap an enolate efficiently, the regenerated enolate could then be alkylated in a separate step (Scheme 4). Based on steric

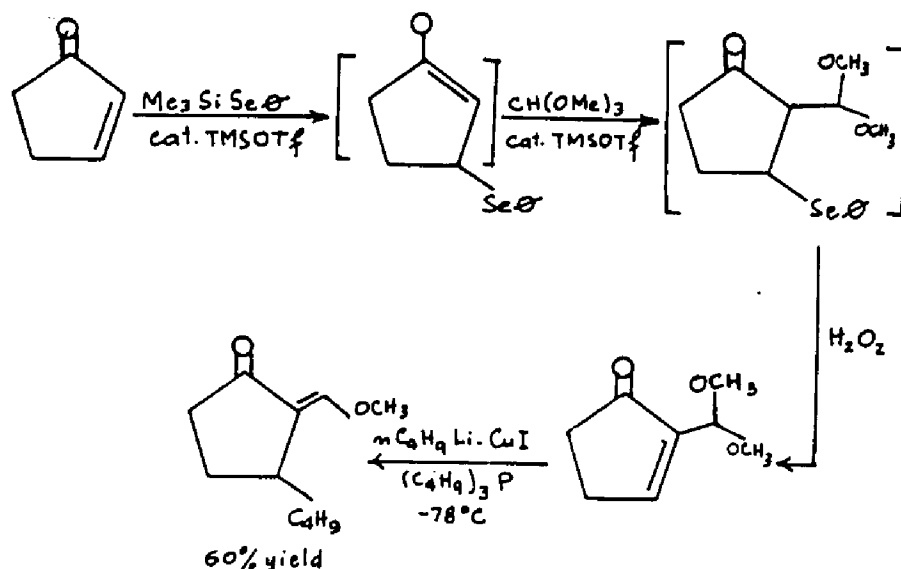
Scheme 4.



considerations the approach was expected to give [24] with a trans stereochemical relationship at carbons 2 and 3. For that reason the authors assumed their product to be the trans isomer.

In 1981, Noyori⁶⁰ devised a one-pot procedure for α -alkoxyalkylation of 2-cyclopentenones which in combination with an organocopper addition reaction provides a new tool for vicinal substitution of carbon groups on enones. The method was based on the efficient conjugate addition of a phenyl silyl selenide to α,β -unsaturated ketones and the aldol-type reaction of enol silyl ethers with acetals or ortho esters (both catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf)). The selenides can be oxidized to selenoxides which undergo ready β -elimination (Scheme 5).

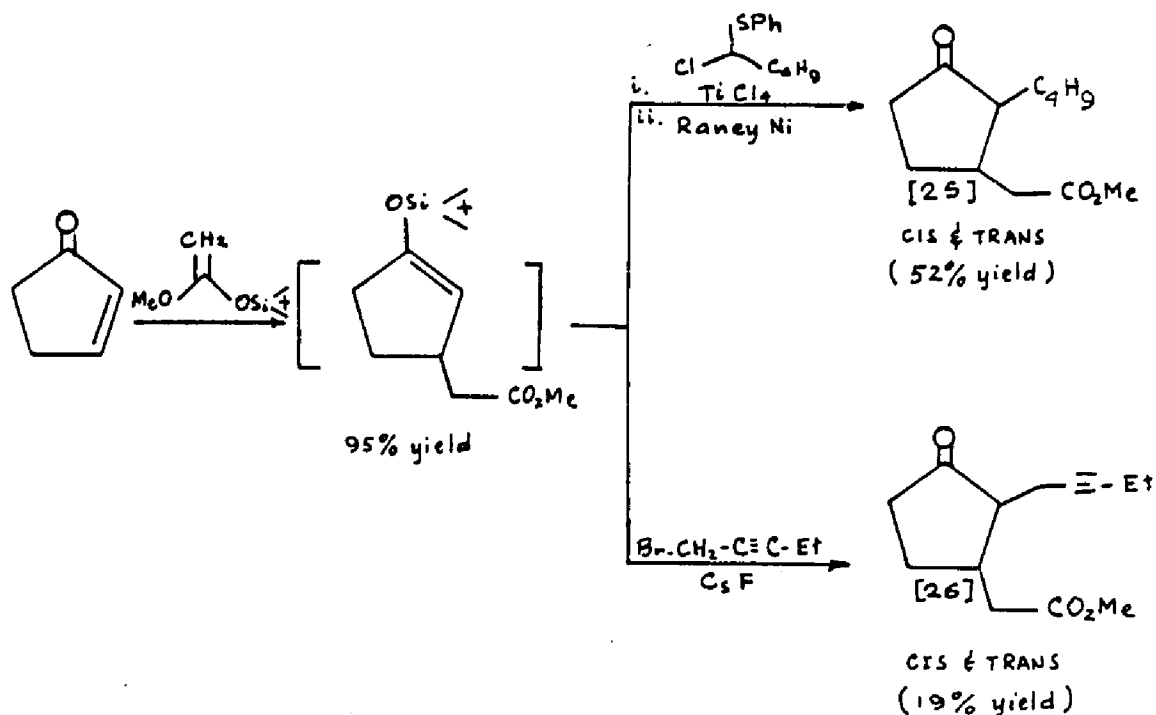
Scheme 5.



In 1982, Tamura⁶¹ and his coworkers described conjugate addition of ketene silyl acetals to α,β -unsaturat

ed carbonyl compounds in acetonitrile to give a quantitative yield of the corresponding methyl(3-trialkyl-siloxyalk-2-enyl)acetates. Subsequent site-specific electrophilic substitution yielded the corresponding 2-substituted 3-(alkoxycarbonylmethyl)cyclopentanones (Scheme 6). The cis/trans mixtures of [25] and [26] were separately heated in Et₃N to produce material enriched in the trans isomer (g.l.c. purity > 95% in each case).

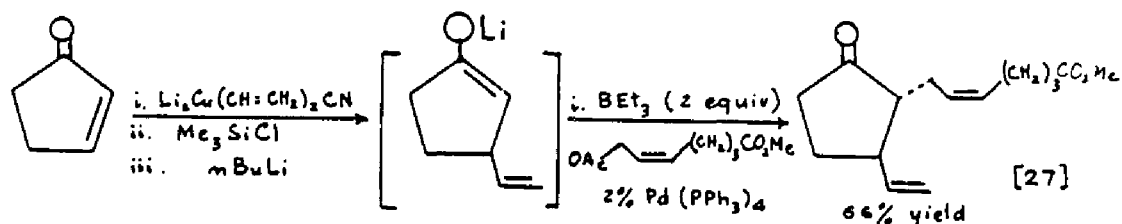
Scheme 6.



In 1985, Negishi⁶² and Luo developed a highly stereo- and regioselective synthesis of trans 2-allyl-3-alkenylcyclopentanones [27] (90% g.l.c purity) via Pd-catalyzed reaction of borate salts of lithium cyclopentenolates with

(Z)-allylic acetates, which promised to provide a solution to most of the following problems: i. low product yields in part due to loss of allyl stereochemistry and of ring regiochemistry, ii. the requirement for an excess, typically a three-to five-fold excess, of labile (Z)-allylic iodides or bromides (Scheme 7).

Scheme 7.



5. 2-Alkyl-2-cyclopentenone precursors: conjugate

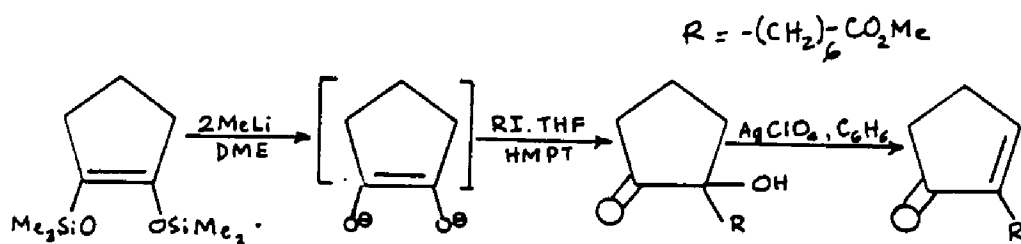
1,4-addition approaches:

2-Alkyl-2-cyclopentenones are, in general, useful starting materials in the synthesis of the prostaglandin assembly via conjugate addition of organometallic derivatives.⁶² The 2-alkyl-2-cyclopentenones can be prepared from enediol-bis-trimethylsilyl ether, furanone, cyclopent-

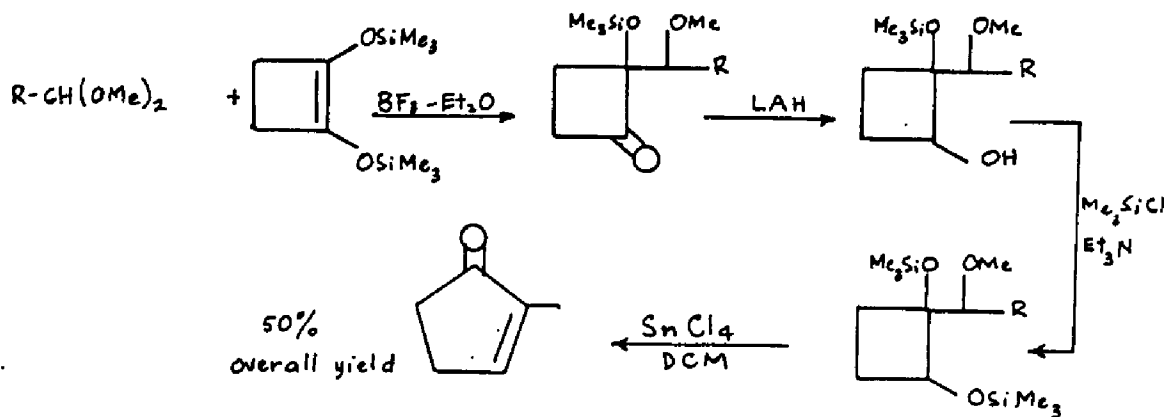
tanoic acid, 1,4-diketones and β -dicarbonyl compounds, as described in the following paragraphs.

Wakamatsu⁶⁴ and his co-workers have demonstrated a new simple preparation of 2-alkylcyclopentenones by converting an enediol-bis-trimethylsilyl ether into its 1,2-ene-diolate, which was followed by alkylation and dehydration as shown in Scheme 8.

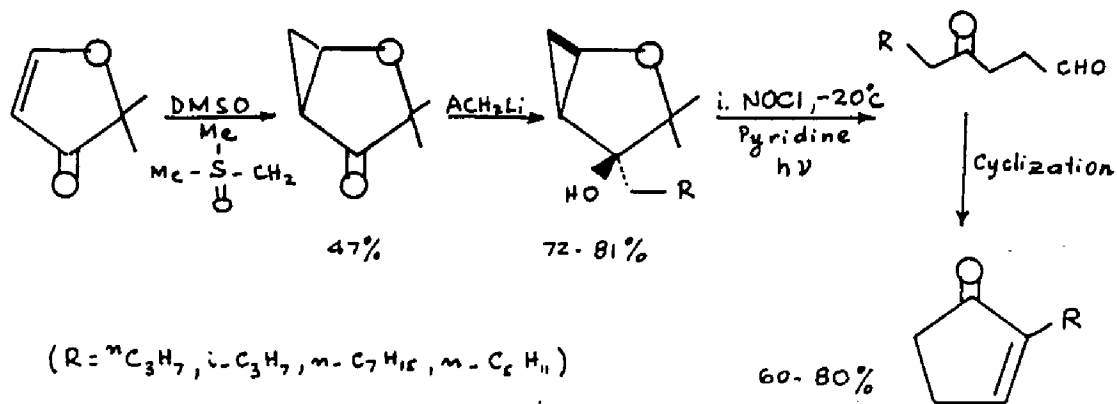
Scheme 8.



Kuwajima and his co-workers⁶⁵ have employed an aldol-type coupling of acetals with enediol-bis-trimethylsilyl ether in the presence of $BF_3 \cdot Et_2O$ catalyst. Acid catalyzed ring expansion reactions of cyclobutane derivatives bearing a vicinal substituted diol group gave α -vinyl substituted cyclopentenones in good yield (Scheme 9).

Scheme 9.

An efficient synthesis of 2-substitutedcyclopentenones was reported by Baldwin and Blomquist.⁶⁶ Key reactions

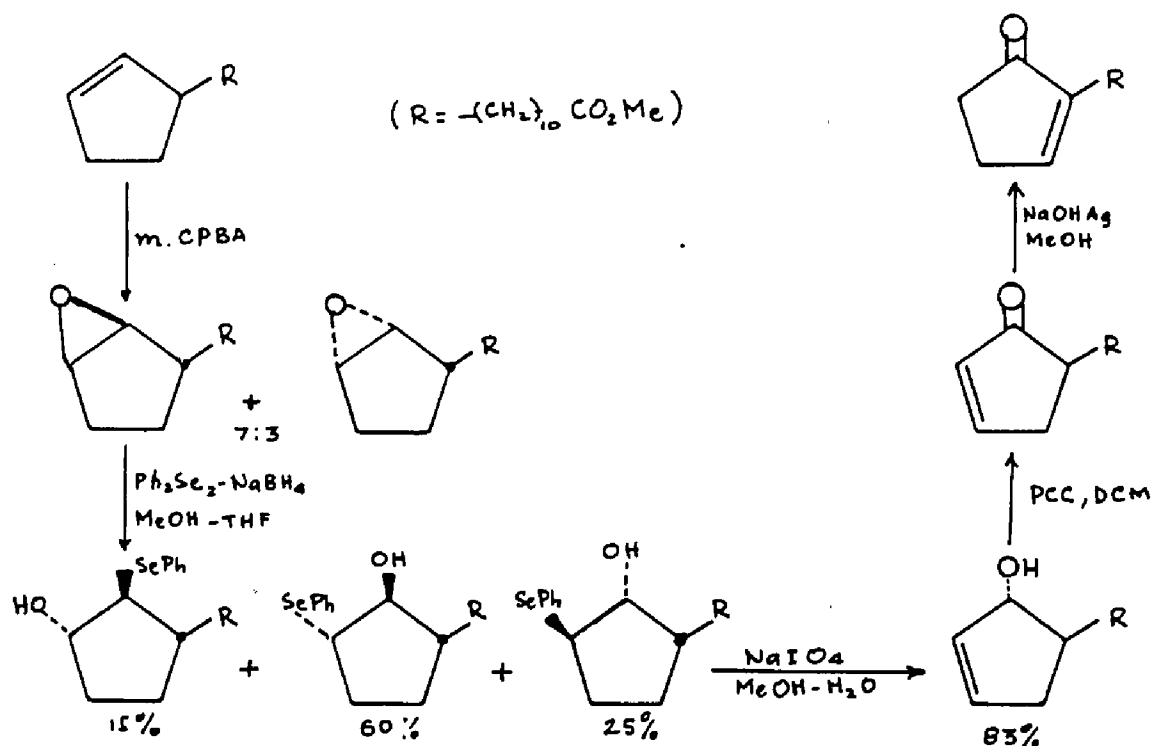
Scheme 10.

were cyclopropanation of 2,2-dimethyl-3-(2H)-furanones and

subsequent conversion to the cyclopentenones by Barton oxidative fragmentation (Scheme 10).

Barreiro and Gomes ⁶⁷ have used an abundant cyclopenten-containing natural product to synthesize 2-alkylcyclopentenone. (Scheme 11).

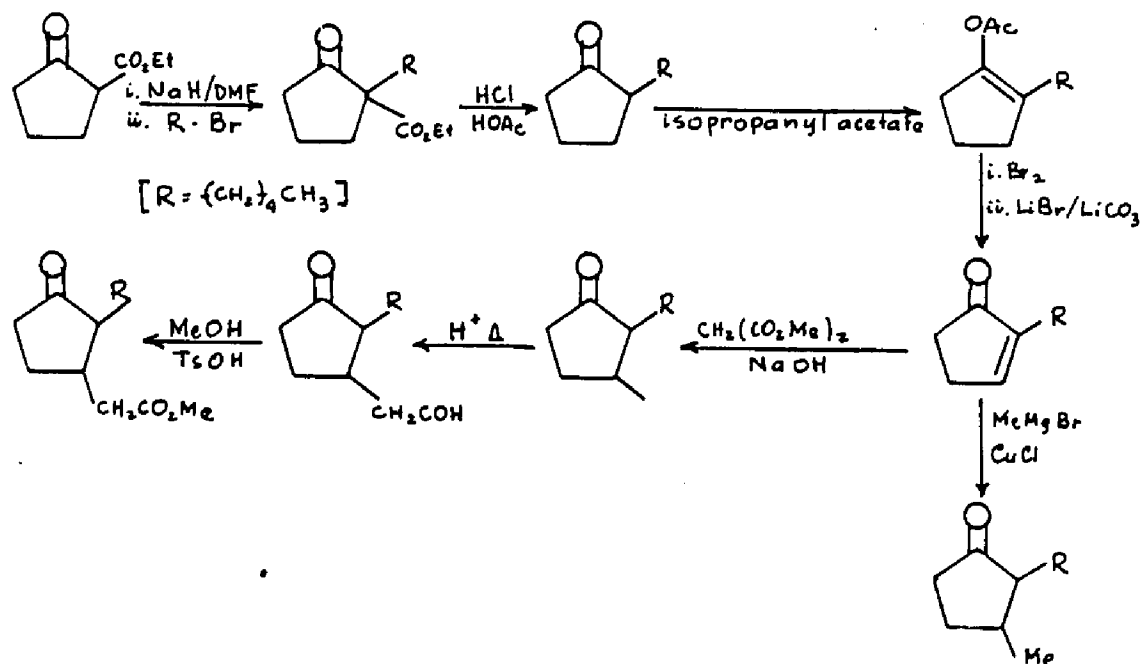
Scheme 11.



Ikan and David ⁶⁸ have described efficient five-step and seven-step syntheses of α, β -dialkylcyclopentanones. The precursor in the synthetic scheme was 2-carboethoxycyclopentanone which underwent alkylation specifically between the two carbonyl groups and gave product free

from polyalkylation. The advantages of the synthesis were that the starting materials were relatively inexpensive and easily accessible and the overall yields of the products were satisfactory (Scheme 12).

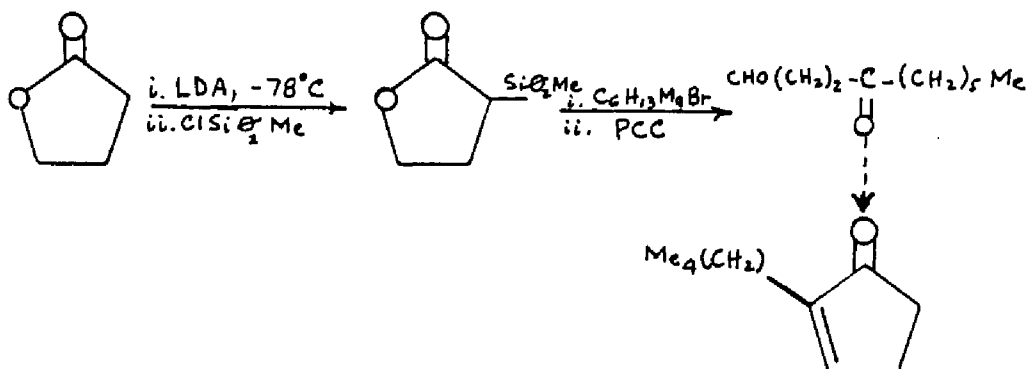
Scheme 12.



The most common routes for preparing 2-alkylcyclopentenones are based on 1,4-dicarbonyl compounds ⁶⁹. Although many methods to make 1,4-diketones are available, there are relatively few methods for the preparation of 4-ketoaldehydes. Recently Larson ⁷⁰ and his research group have utilized the reaction of α -(diphenylmethylsilyl)- γ -

butyrolactone with hexylmagnesium bromide, followed by oxidation with PCC (pyridinium chloro chromate), to yield 4-oxodecanal (Scheme 13).

Scheme 13.



It is known that organocopper conjugate addition to 2-alkylcyclopent-2-en-1-ones is the key carbon-carbon σ -bond forming step in some very successful and widely used α, β -dialkylcyclopentanone syntheses. This organocopper reaction proceeds chemospecifically without consuming unconjugated carbonyl functionality, and protonation of the enolate intermediate generated via this organocopper conjugate addition leads exclusively to the thermodynamically stable trans-orientation⁷¹ of the two adjacent carbon side chains.

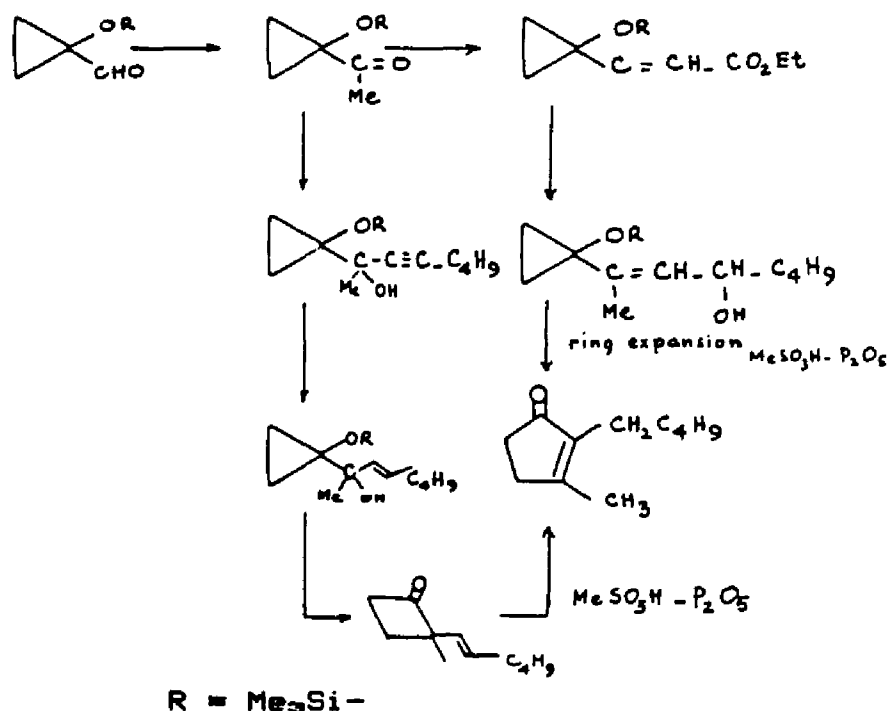
6. 2,3-Dialkyl-2-cyclopentenone precursors:

reduction of -C=C- approach

Since numerous methods for the preparation of the

title compounds have been surveyed,⁷² this section attempts to review some of the recent advances by which 2,3-dialkylcyclopentenones can be prepared and then reduced to provide 2,3-dialkylcyclopentanones. In 1985, Salaun

Scheme 14.

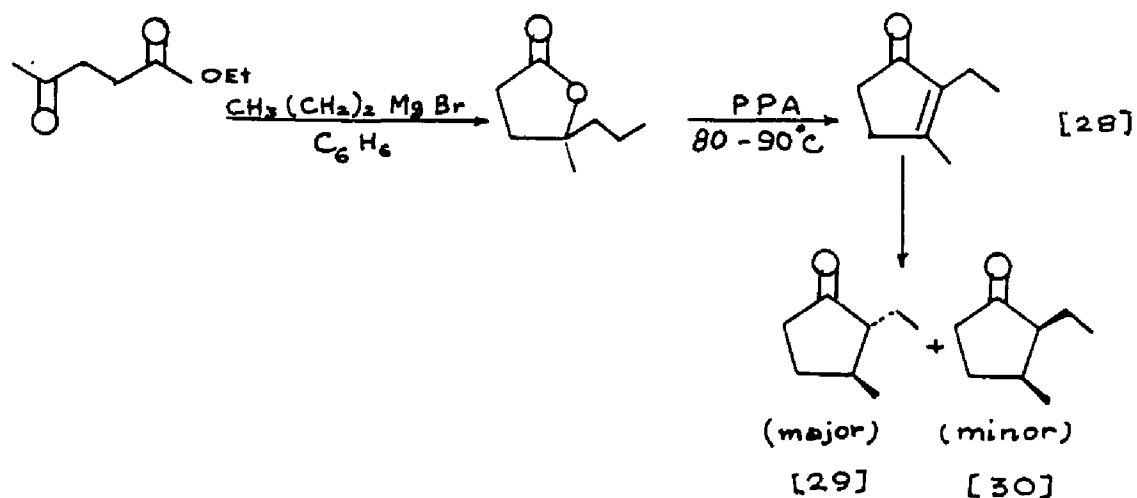


and Oliver reported that silylated 1-vinylcyclopropanols can undergo acid-induced ring expansion^{73,74} via the intermediacy of cyclobutanones into cyclopentenone derivatives (Scheme 14).

In the same year, Paquette and Barth⁷⁵ prepared 2,3-disubstituted cyclopentanones from 2,3-disubstituted cyclopentenone as shown below (Scheme 15). The enone [28] was subjected to catalytic hydrogenation. The distribution of [29] and [30] was found to be highly dependent

upon the conditions of reduction, which is a direct result of the sensitivity of the cis isomer to epimerization. Samples highly enriched (90%) in [30] were readily transformed

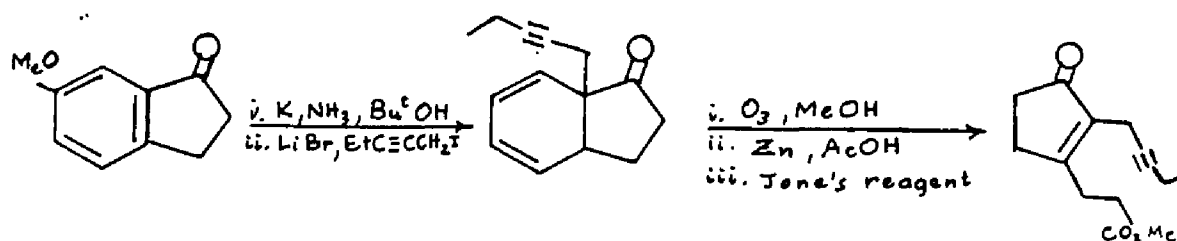
Scheme 15.



into mixtures dominated by [29], especially when acidic reagents were involved.

In 1986, Moody and his associates ⁷⁶ demonstrated the synthesis of a 2,3-disubstituted cyclopent-2-en-1-one

Scheme 16.



by a route which involved reductive alkylation and ozonolysis from 6-methoxyindanone in an overall yield of 29% (Scheme 16).

II. SYNTHESIS OF 5-MEMBERED RING PHEROMONE ANALOGS:

A. Preparation of 2-(5-acetoxypentyl)-3-ethylcyclopentanone:

Two of three approaches which have been reviewed above for syntheses of 2,3-dialkylcyclopentanones were studied for the preparation of 2-(5-acetoxypentyl)-3-ethylcyclopentanone. (i) In the conjugate addition - alkylation approach starting from 2-cyclopentenone, Posner's one-pot reaction was examined but failed due to lack of reactivity of the resultant enolates toward alkyl halides. In order to accomplish the reaction, the enolate ion was trapped by Me_3SiCl as in Patterson and Fried's method. (Methyl chloroformate is also a trapping reagent; it was not used in the 2-(5-acetoxypentyl)-3-ethylcyclopentanone synthesis because of its high toxicity as compared to Me_3SiCl .) Patterson and Fried's procedure is the method of choice. In their method, fewer steps were required, satisfactory yield was obtained, and no catalyst was used. This method seemed to be the most convenient for preparing the product via conjugate addition - alkylation reactions. (ii) In the conjugate addition approaches starting from 2-alkyl-2-cyclopentenone, Ikan and David's

routes were followed since the starting materials for 2-alkyl-2-cyclopentenone are inexpensive, easily accessible and overall yields of the product are satisfactory. In comparison with Ikan and David's route, starting materials for some of the other possibilities were not commercially available, eg. bis-trimethylcyclobutene (Kuwajima's route), bis-trimethylcyclopentene (Wakamatsu's method) and Barreiro and Gomes' method was more lengthy. Thus routes from 2-cyclopentenone and 2-alkyl-2-cyclopentenone were chosen from those methods reviewed above to synthesize 2-(5-acetoxypentyl)-3-ethylcyclopentanone [37]. The differences in stereochemistry of [37] as obtained from these various route is a matter of considerable concern. The most stereoselective 2-alkyl-2-cyclopentenone route will be the most desirable.

1. Route from 2-cyclopentenone:

Although 2-cyclopentenone is commercially available, its cost is high, especially when it is to be used as the basic starting material in a multi step synthetic scheme. Thus preparation of 2-cyclopentenone from an inexpensive material, cyclopentanone, was explored in some detail and is described below.

a. Preparation of 2-cyclopentenone:

Previous syntheses of 2-cyclopentenone have involved the elimination of HCl from 2-chlorocyclopentanone⁷⁸ or its ketal,⁷⁹ the oxidation of 3-chloro⁸⁰ or 3-hydroxy cy-

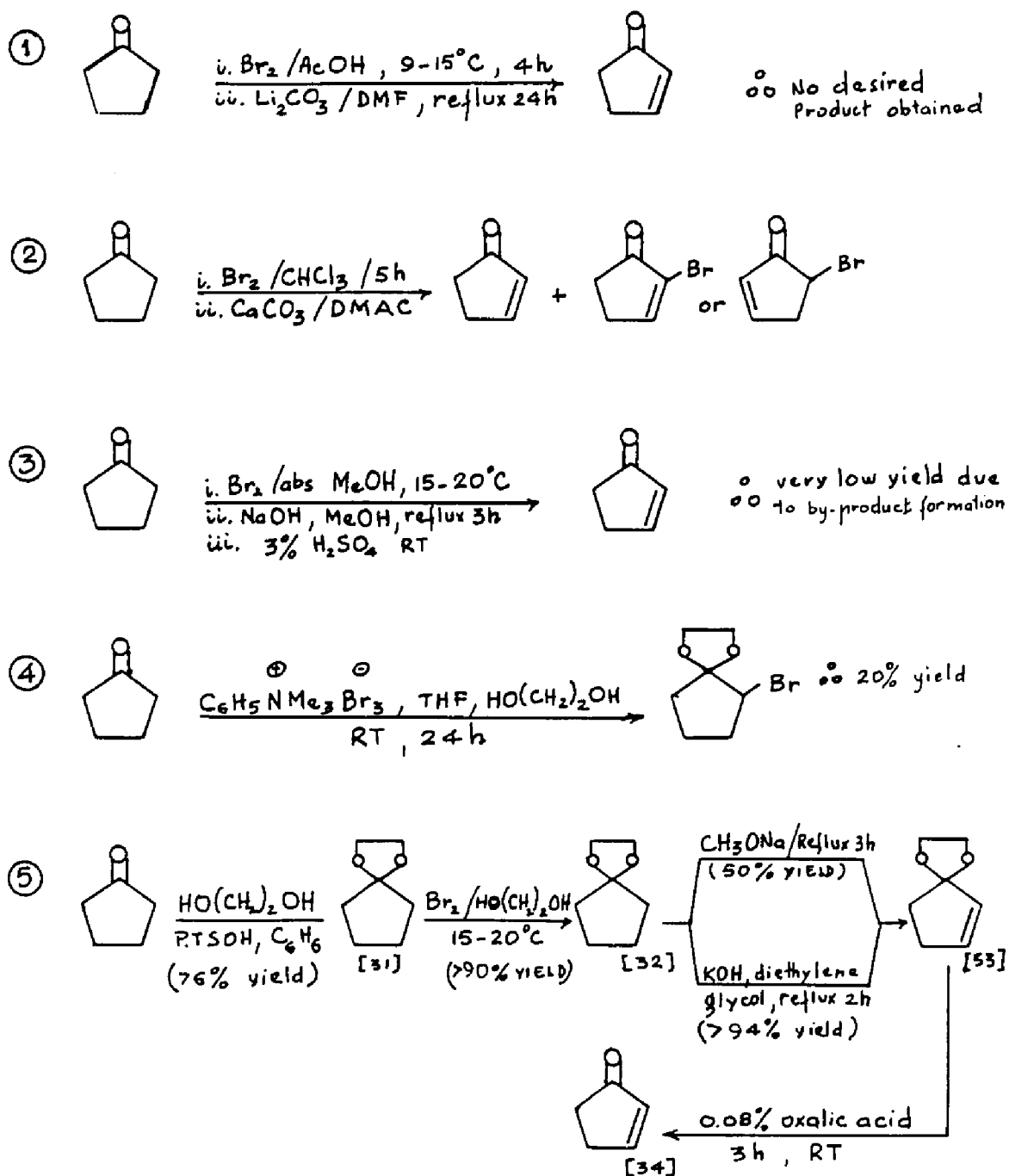
clopentene,⁸¹ as well as the direct oxidation of cyclopentene with H_2O_2 .⁸² Cyclopentanone has also been prepared from cyclopentenediols,⁸³ 1-dicyclopentadienol,⁸⁴ palladium (II)-catalyzed dehydrosilylation of 1-trimethylsiloxy-cyclopentene,⁸⁵ and thermolysis-hydrolysis of 2-norbornanone.⁸⁶ However, a convenient synthesis of 2-cyclopentenone, which involves bromination, then dehydrobromination is examined here. The process may be carried out either on cyclopentanone itself or on a ketal derivative. Several procedures which have been reported in the literature, but which gave poor results in our hands, are outlined in Scheme 17.

Cyclopentanone was treated with Br_2 in acetic acid at $9-15^\circ\text{C}$,⁸⁷ followed by Li_2CO_3 in DMF at reflux (Entry 1; Scheme 17). The dehydrobromination did not occur as shown by the absence of ^1H NMR signals of 2-cyclopentenone in the crude product. The failure of the reaction might be due to the decomposition of the starting material. Indeed, the bromocyclopentanone turned from a yellow liquid to a dark brown solid after storage at room temperature overnight. Using freshly prepared bromo compound did not cure the problem.

Bromination of cyclopentanone at room temperature was carried out in chloroform containing Br_2 , followed by elimination of HBr with DMF and CaCO_3 .⁸⁸ This process provided a mixture of cyclopentenone and bromocyclopenten-

one according to $^1\text{H-NMR}$ and mass spectral analyses (Entry 2, Scheme 17). The procedure is in some instances ineffi-

Scheme 17.



cient and tedious. The crude bromo ketone in DMAC (N,N'-dimethylacetamide) was added over 5 min. to a well-stirred, refluxing slurry of CaCO_3 /DMAC. After 5 min. more, the reflux condenser was replaced with a distillation head and DMAC removed as rapidly as possible by judicious reduction of pressure until a desired volume²⁹ of DMAC remained. The reaction mixture was cooled then worked up.

Since it is difficult to control the monobromination of cyclopentanone in acetic acid and chloroform, Marquet and Gaudry²⁹ have recommended methanol as a brominating solvent since dibromination is very slow in methanol. This contrasts with the behavior in other solvents such as ether or CCl_4 where larger amounts of dibromoketones are always present even when one equivalent of bromine is used.

An attempt to prepare 2-cyclopentenone³⁰ from cyclopentanone was carried out by following the sequence: i. bromination with Br_2 in absolute methanol at $15 - 20^\circ\text{C}$, ii. dehydrobromination with NaOH in absolute methanol under reflux for 3 h, and iii. hydrolysis of the bromocyclopentanone ketal formed in ii with 3% H_2SO_4 for 3 min (Entry 3, Scheme 17). 2-Cyclopentenone was obtained in very low yield due to formation of by-products such as aldol condensation or dimerization products. Evidence for formation of the latter was seen in the mass spectral ana-

lysis of the product mixture. One compound had a M^+ ion at m/e 164. Indeed, Bellamy²¹ has reported the dimerization of 4,4-dimethylcyclopent-2-enone is catalyzed by base.

Another attempt to brominate and ketalize cyclopentanone²² in one pot according to Chandrasekaram's method yielded only 20% of the α -bromocyclopentanone ethylene ketal. (Entry 4, Scheme 17). The remainder of the reaction mixture was an unidentified, dark brown solid. Thus all of the above attempts were unsatisfactory.

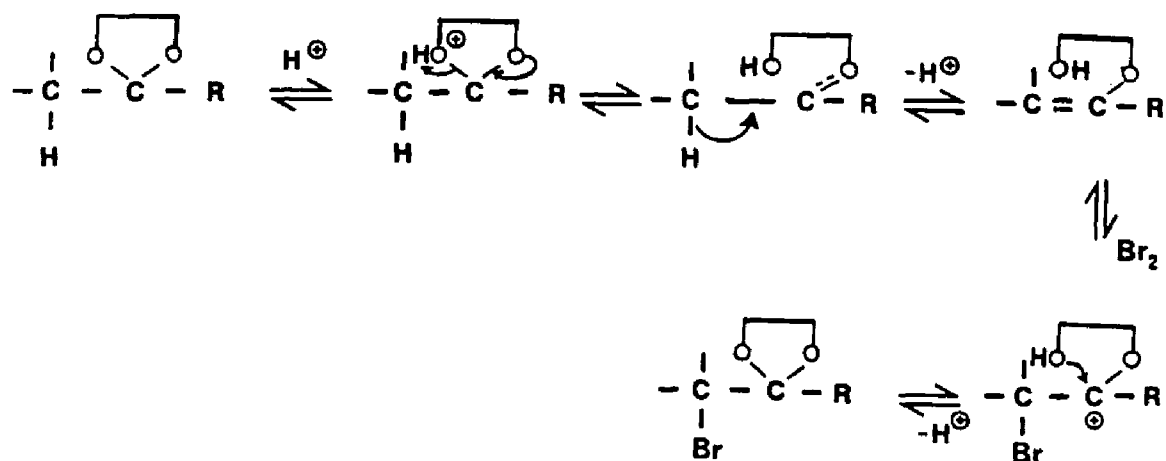
After these unsuccessful attempts, 2-cyclopentenone was prepared in satisfactory yield by the following strategy (Entry 5, Scheme 17): i. ketalization of cyclopentanone, ii. bromination of cyclopentanone ethylene ketal, iii. dehydrobromination of α -bromocyclopentanone ethylene ketal, iv. hydrolysis of 2-cyclopentenone ethylene ketal. This dehydrobromination method can avoid the self condensation and Favorski reactions of α -bromocyclopentanone.

i. Cyclopentanone was reacted with ethylene glycol in the presence p-toluenesulfonic acid catalyst to form [31] in 42-76% yield depending the on method applied. In Godefroi's method,²³ the reaction mixture is refluxed for 72 h with two interruptions between reflux, followed by two washings, resulting in a 42% yield. An explanation for the two interruptions is based on the assumption that an acetalization process can be driven to completion by adding more of the alcohol and the catalyst. In Eliel and Daig-

nault's method,²⁴ the reaction mixture is continuously refluxed for 12 h or one week to give 62% or 76% yield, respectively.

ii. Chapman²⁵ has reported that attempted bromination of [31] with pyridinium bromide perbromide, trimethylphenyl ammonium perbromide, and with molecular bromine in a range of solvents all failed. However, treatment of [31] with Br₂ in dry ethylene glycol following the carefully developed procedure of Garbisch,²⁶ is found to lead to an excellent yield (93%) of [32] based on ¹H-NMR. It was found advantageous to proceed directly to the dehydrobromination. Thus an isolated yield of [32] cannot be reported. The dibromination is difficult to accomplish even at increased temperature because after one equivalent of bromine has reacted, further reaction with bromine is visibly much slower, and during the bromination in ethylene glycol, the bromo ketal product generally separates from solution.

Scheme 18



Marquet and his co-workers ²⁶ have proposed the mechanism of bromination of cycloalkanone ethylene ketal to be that shown in Scheme 18 above.

iii. 2-bromocyclopentanone ethylene ketal undergoes smooth dehydrobromination in strong base (KOH/ diethylene glycol) to yield 80% of the isolated [33], and 20% of a mixture of [32] and [34] according to GC analysis. The formation of [34] may be explained by the presence of NH_4Cl in the reaction mixture.

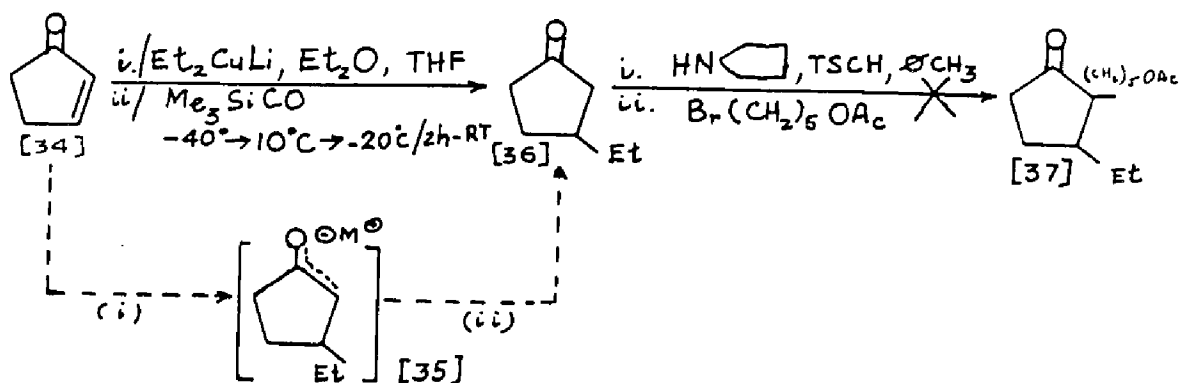
iv. Mild hydrolysis of [33] with aqueous oxalic acid frees the carbonyl group and provides [34] (76% yield) along with [33] and its isomers (24% yield). During the work-up of the reaction mixture, use of NaHCO_3 for neutralization gives higher yield (76%) than does CaCO_3 (63%). This hydrolysis procedure produces a better yield of [34] than does Barbisch's method (65% yield of [34], using 3% H_2SO_4 and a reaction time of 5 min.) ²⁰

b. Preparation of 2-(5-acetoxypentyl)-3-ethylcyclopentanone [37]:

The 1,4-conjugate addition of lithium diethylcuprate to 2-cyclopentenone gave the enolate [35]. An unsuccessful attempt to trap the resulting enolate [35] with Me_2SiCl

afforded 3-ethylcyclopentanone [36]. Compound [36] in toluene was treated with pyrrolidine in the presence of p-toluenesulfonic acid as catalyst, followed by addition of 5-bromopentyl acetate. The reaction failed to produce [37]. [36] was recovered, whereas 5-bromopentyl acetate was not. Frequently, the alkylation of enamines with simple alkylating agents is not a good preparative method because the major reaction is N-alkylation rather than C-alkylation.⁹⁷ The situation is similar to C- or O- alkylation of enolate anions; however, the enamine, being uncharged, has no cation to shield the nitrogen from attack by the alkylating agent. Also, the nitrogen atom of enamines is softer (more polarizable) than the corresponding enolate oxygen atom. Both of these factors apparently contribute to making N-alkylation a serious competing reaction in attempts to alkylate enamines at carbon. Thus the Stork enamine reaction is quite useful for particularly active alkyl halides such

Scheme 19.



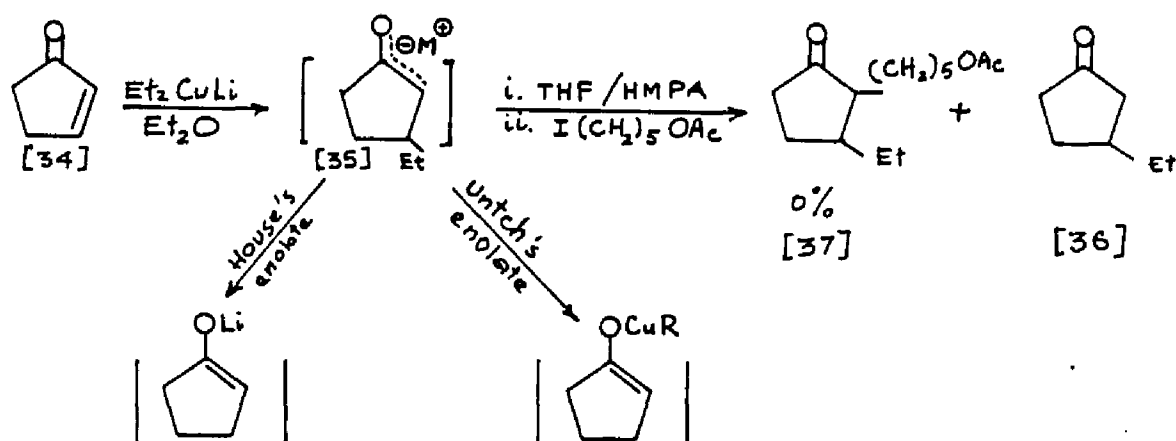
as allyl, benzyl and propargyl halides, but is not very serviceable for ordinary primary and secondary halides (Scheme 19).

One of the attractive routes to [37] is the one-pot reaction²⁴ involving organocopper conjugate addition to 2-cyclopentenone followed by alkylation. It is based on the fact²⁵ that the cuprate-generated enolate which is present in the reaction mixture in large amount (>>70%) prior to protic quench, can perform α -alkylation²⁶, especially when HMPA is added prior to addition of the alkylating reagent. Conjugate addition of Et_2CuLi (2 equiv.) to 2-cyclopentenone (1 equiv.) followed by the addition of HMPA and 5-iodopentyl acetate (8 equiv.) gave none of the desired product [37]; only the addition product [36] was formed. According to Coates^{26b} the unreactivity of the copper-lithium enolate intermediate is presumed to be a consequence of increased covalency of the copper-oxygen as opposed to the lithium-oxygen bond.

Based on the studies of Untch and Davis^{26a}, an enolate first formed via cuprate conjugate addition is complex in nature and may involve copper in some way, since no alkylation occurs even with either methyl iodide or allyl iodide. The addition of HMPA to the reaction medium provides a different enolate. However, this enolate

undergoes proton transfer at a rate faster than regioselective alkylation and thus renders this route to the synthesis of [37] ineffective. House and Wilkins¹⁰⁰ have provided convincing evidence that the intermediate formed by the addition of Me_2CuLi to 3-methylcyclohex-2-enone is a lithium enolate. Nevertheless, the investigation of Davis and Untch⁹⁹ indicated that the nature of the intermediate formed by cuprate addition depends upon the structure of the alkyl group, the enone, and perhaps the solubilizing ligand used [$\text{OP}(\text{OMe})_3$] (Scheme 20).

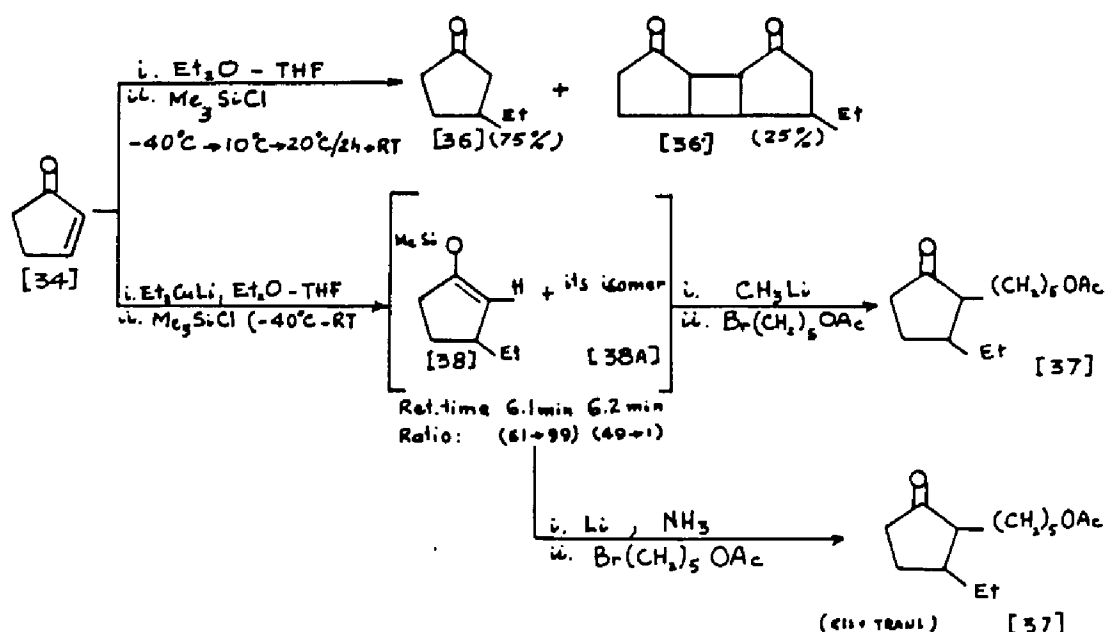
Scheme 20.



After two initial attempts to prepare 2-(5-acetoxypentyl)-3-ethylcyclopentanone were unsuccessful, a further study was carried out in the presence of Me_3SiCl . Et_2CuLi was conjugatively-added to 2-cyclopentenone, and the resulting enolate was trapped with Me_3SiCl to provide the

intermediate which appeared as two isomers, [38] and [38A] in a 90:10 ratio, in 65% yield. However, the product is unstable at room temperature (23°C). If left at 23°C overnight, it turned from a colorless liquid to slightly yellow and its vinylic proton peak in the ^1H NMR diminished gradually. However, [38] could be stored in a refrigerator (5°C) for a month. It should be noted that yields in the direct enolate ion trapping method depend on temperature. If after the addition of Me_3SiCl to the enolate at -40°C, the cold bath is removed at once, and the reaction mixture warmed to room temperature, [38] is obtained. In contrast, [36] and [36'] were formed in a 75:25 ratio (based on GC) instead of [38] if the reaction mixture was warmed to 10°C after the cold bath was removed then

Scheme 21.

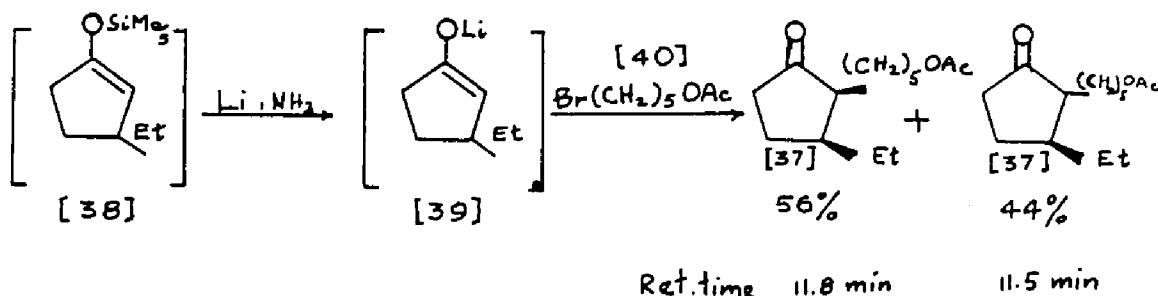


recooled to -20°C for 2 h, then warmed to room temperature (Scheme 21). The reason for this difference is not clear since Me_3SiCl could have been expected to capture the enolate rapidly.

The alkylation route in which the silyl enol ether [38] is converted to lithium enolate by MeLi , followed by an alkylation with 5-bromopentyl acetate [40] did not result in formation of 2-(5-acetoxypentyl)-3-ethylcyclopentanone [37]. [40] was recovered, and [36] was formed, according to $^1\text{H-NMR}$ and MS analysis.

Binkley and Heathcock¹⁰¹ have demonstrated that lithium enolates generated from trimethylsilyl enol ether with lithium amide undergo regiospecific alkylation in a mixture of liquid NH_3 -THF where proton transfer is an insignificant side reaction (NH_3 is too weak an acid

Scheme 22.

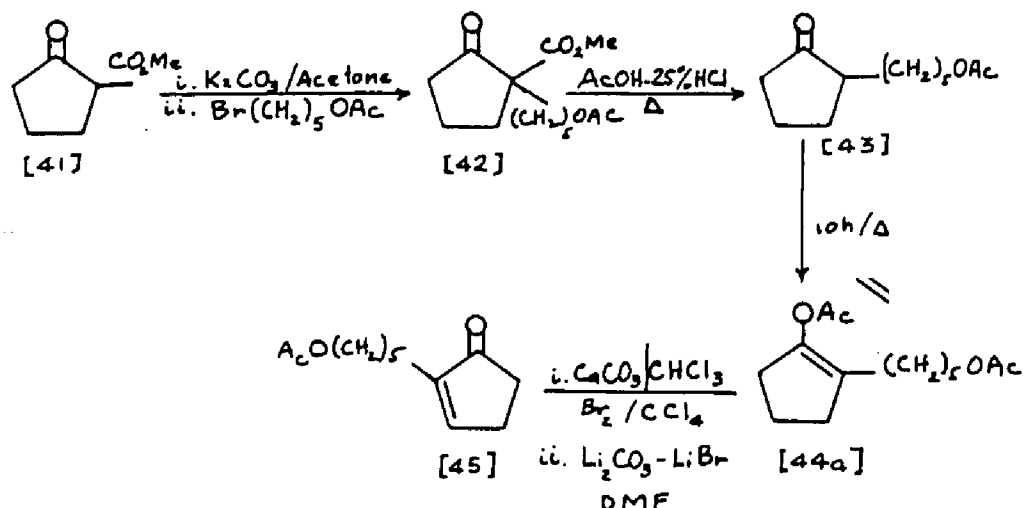


to protonate the enolate, which should therefore maintain its structural integrity) (Scheme 22). The enolate [39] was generated regioselectively from the silyl enol ether [38] with LiNH_2 in $\text{NH}_3\text{-THF}$ and then alkylated with [40] (4 eq.) to provide a 41% yield of a 56:44 ratio of the cis and trans isomers of [37] (ret. time 11.8 and 11.5, respectively). In all runs, cis-[37] was produced in an amount equal to or greater than trans-[37]. Stereochemical assignments for the products will be discussed in a later section.

2. Route to α, β -dialkylcyclopentanone via 2-alkylcyclopent-2-en-1-one:

2-(5-Acetoxypentyl)cyclopent-2-en-1-one [45] was prepared conveniently from 2-carbomethoxycyclopentanone [41] as indicated in Scheme 23. The alkylation of [41] in

Scheme 23.



the presence of K_2CO_3 /acetone, which was followed by the addition of 5-bromopentyl acetate [40], afforded [42] in good (54-77%) yield. When the reaction mixture was refluxed longer and less acetone was used, the yield was higher than with a shorter time and more acetone. The low yield of alkylation could be explained by incomplete reaction, since [41] and [40] were recovered in larger amounts when more acetone was used making the alkali concentration lower. Saponification of β -keto ester such as [42] is often complicated by competing attack of the hydroxide anion at the ketone function, leading to ring cleavage rather than saponification, especially in cases in which the α -position is disubstituted¹⁰². For this reason the hydrolysis and decarboxylation of [42] were carried out by refluxing in aqueous acid (AcOH/25% HCl) to afford [43] in 75% yield. This reaction was slow for the long chain alkyl derivatives, probably because of their poor solubility. However, use of acetic acid as solvent allowed a smooth reaction.

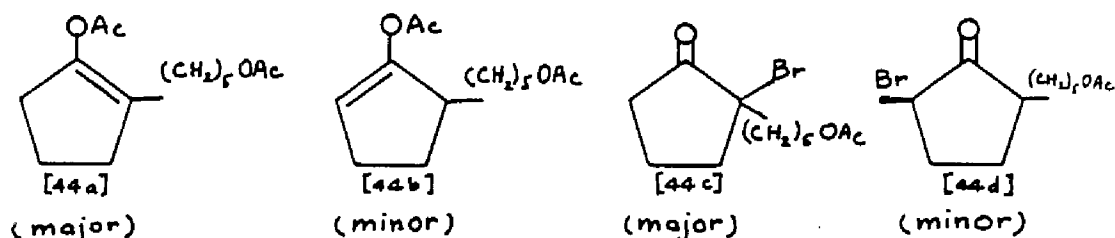
The conversion of cyclopentanone [43] to cyclopentenone [45] was accomplished by halogenation of enol acetate [44] and subsequent dehydrohalogenation. Direct halogenation of [43] with sulfuryl chloride or elemental bromine were not clean reactions, leading to mixtures of starting ketone [43] with monohalogenated and polyhalogenated ketones.

Bromination of [44] was cleaner. Enol acetylation of [43] with refluxing acetic anhydride and *p*-toluene-sulfonic acid catalyst proceeded to 97% completion (after 10 h) and gave a mixture of two isomers [44a] and [44b] in the ratio of 98:2 as shown by GC (retention times of [44a] and [44b] are 8.18 and 8.20 min, respectively). (However, purification of enol acetate [44] by column chromatography on silica gel, eluting with 0-2% ethyl acetate/hexane (v/v) gave only 58% isolated yield, probably because the acidic character of silica gel caused the hydrolysis of the enol acetate to cyclopentanone [43]. Even technical grade DCM, with a trace of water and HCl can turn clear enol acetate cloudy as hydrolysis takes place giving the starting material back). With perchloric acid as catalyst, the same isomer composition was rapidly (15 min) attained at room temperature, but the reaction could not be pushed to more than 90% completion, possibly because the by-product acetic acid could not be removed.

Bromination of the enol acetate was accomplished in a three phase reaction medium. Addition of a CCl_4 solution of bromine to a mixture consisting of a chloroform solution of enol acetate [44a] and [44b] and an aqueous suspension of CaCO_3 resulted in a rapid uptake of 1 equivalent of Br_2 ; any excess of Br_2 persisted until the mixture was worked up. The crude bromoketones [44c] and [44d] (identified by $^1\text{H-NMR}$) were then dehydrobrominated without delay (Scheme

24). Of the several dehydrobromination procedures investigated, lithium bromide and lithium carbonate in refluxing dimethylformamide or calcium carbonate in hot dimethylacetamide were found to be most effective^{102b}. Treatment of

Scheme 24.



the crude bromoketones [44c] and [44d] with LiBr/Li₂CO₃ in DMF gave 2-(5-acetoxypentyl)cyclopent-2-enone [45] in 52% yield as a colorless oil. It should be noted that the procedure described above was not the best method to prepare unsubstituted cyclopentanone from cyclopentanone (see Entries 1 and 2, Scheme 17).

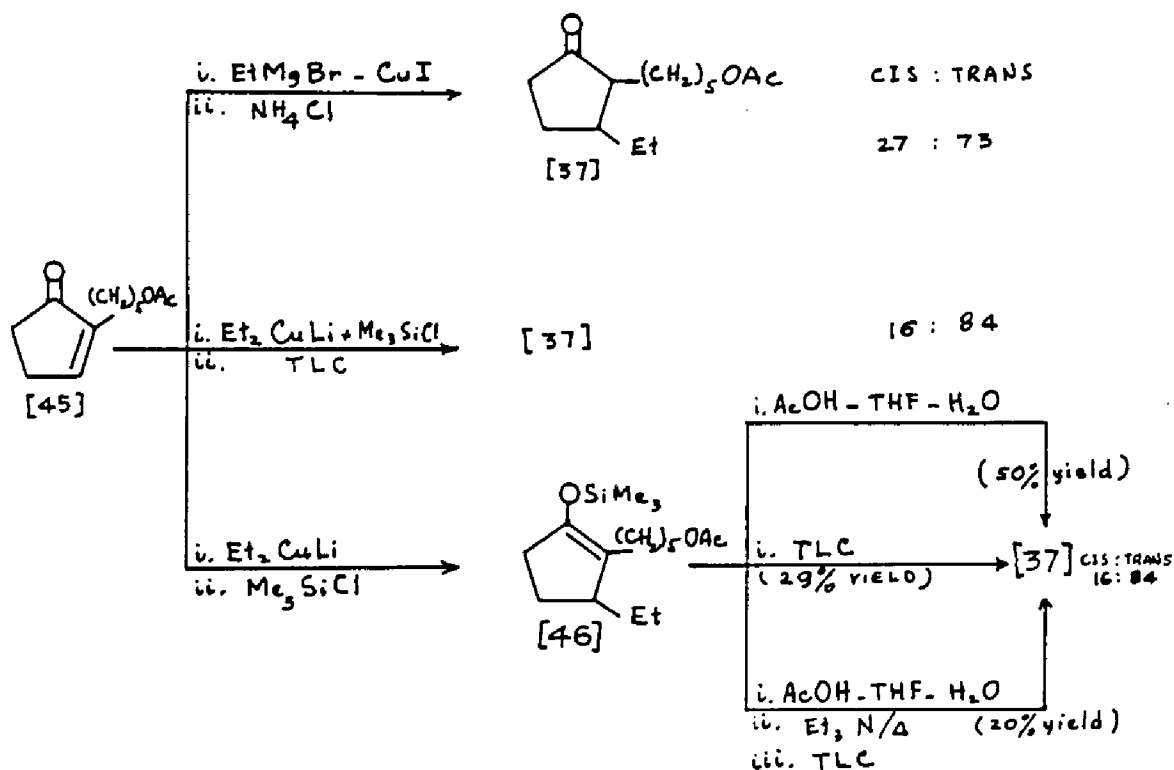
After preparing [45], the next step in the overall synthetic scheme requires conjugate addition of the ethyl group at the β -carbon atom of [45]. The conjugate addition of organocopper reagent to [45] is analogous to the key C-C bond formation step in some very successful syntheses. It involved conjugate addition of the two-carbon "lower" side chain as an homocuprate reagent (Et₂CuLi) to

the substrate [45]. This organocuprate reaction proceeds chemospecifically, and the protonation of the enolate intermediate generated via this organocopper conjugate addition leads predominantly to the thermodynamically stable trans orientation of the two adjacent carbon side chains.^{103c} A recent communication¹⁰⁵ describes the use of a combined organocuprate- Me_3SiCl reagent for conjugate addition to α, β -unsaturated ketones. Organocuprates are known to be the reagents of choice for the efficient 1,4-transfer of an alkyl group to an α, β -unsaturated carbonyl substrate.¹⁰³ In the classical procedure, the carbonyl compound is added to a cuprate solution and the resulting intermediate enolate is often trapped as its trimethylsilyl enol ether by subsequent addition of Me_3SiCl ¹⁰⁴. However, in many instances, this procedure does not avoid side reactions of the enolate, such as Michael or aldol reactions, which lower the overall yield of the 1,4-addition product. In 1980, in a study of the conjugate addition of organocuprate reagents to unsaturated aldehyde, Normant¹⁰⁵ et al. proposed an alternative procedure, in which Me_3SiCl is added before the enol in order to immediately trap the resulting enolate. This idea was based on the observation that the reaction between Me_3SiCl and R_2CuLi was very slow,¹⁰³ while the 1,4-addition of R_2CuLi to an enol and the O-silylation of the resulting enolate were fast processes. In addition, it was observed that the presence of

Me_3SiCl enhances the rate of the conjugate addition reaction. Using this procedure the yield of the conjugate adduct of Bu_2CuLi to acrolein was increased from 25% to 60%.^{105a}

Trans-3-ethyl-2-(5-acetoxypentyl)cyclopentanone [37] (Scheme 25) was prepared with high stereoselectivity from [45]. Copper-catalyzed conjugate addition of EtMgBr to

Scheme 25.

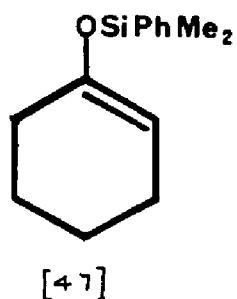


[45] and subsequently treating the resulting cyclopentanone enolate with aqueous NH_4Cl afforded keto ester [37] with 72% stereoselectivity in only 25% yield. Analysis of the crude product showed that it contained 51% of [37], 25% of 2-(5-hydroxypentyl)-3-ethylcyclopentanone, and 24% of starting material (based on GC areas). [37] is a mixture of 2 isomers in which the ratio of cis:trans is 27:73. This reaction is more stereospecific than the alkylation of silyl enol ether as described earlier. It should be noted here that preformed organocopper reagents generally produce 1,4-addition in higher yield (i.e. with less or no 1,2-addition) and greater stereoselectivity than do organocopper reagents prepared in situ.^{103b}

The conjugate addition of Et_2CuLi to [45] in the presence of Me_3SiCl generally gave predominantly trans [37] as in the case of EtMgBr/CuI . Me_3SiCl may play different roles in this reaction. When Me_3SiCl is added after reaction of the cyclopentenone with Et_2CuLi , the only purpose of the Me_3SiCl is to trap the enolate intermediate this route produces [37] with a cis:trans ratio of 16:84 in 33% yield after the intermediate is separated by thin-layer chromatography on silica gel (20% ethyl acetate/hexane as an eluent). When Me_3SiCl is added before the cyclopentenone, it can play the dual roles of trapping and assisting the conjugate addition reaction to form rel-

atively stable silyl enol ether [46] which has been hydrolyzed in aqueous acid, this route gives [37] in 50% yield and the cis:trans ratio is 16:84. The low yield of these conjugate addition reactions can be explained by incomplete reaction (30% of the starting material recovered) and perhaps by the hindrance of approach to the β -carbon offered by substituents at C_{α} .¹⁰⁴

Me_2SiCl assists the conjugate addition reactions by accelerating the reactions and preventing $Z \rightarrow E$ isomerization of enones^{104a}. The silyl enol ether [46] is stable in contrast to [38] which is unstable. The former can be left at room temperature for a few days without a change in its structure; it can also be purified by a flash chromatography on silica gel, eluting with 0-2% ethyl acetate/hexane. The stability of [46] toward silica gel is similar to dimethylphenylsiloxycyclohexene [47]¹⁰⁶

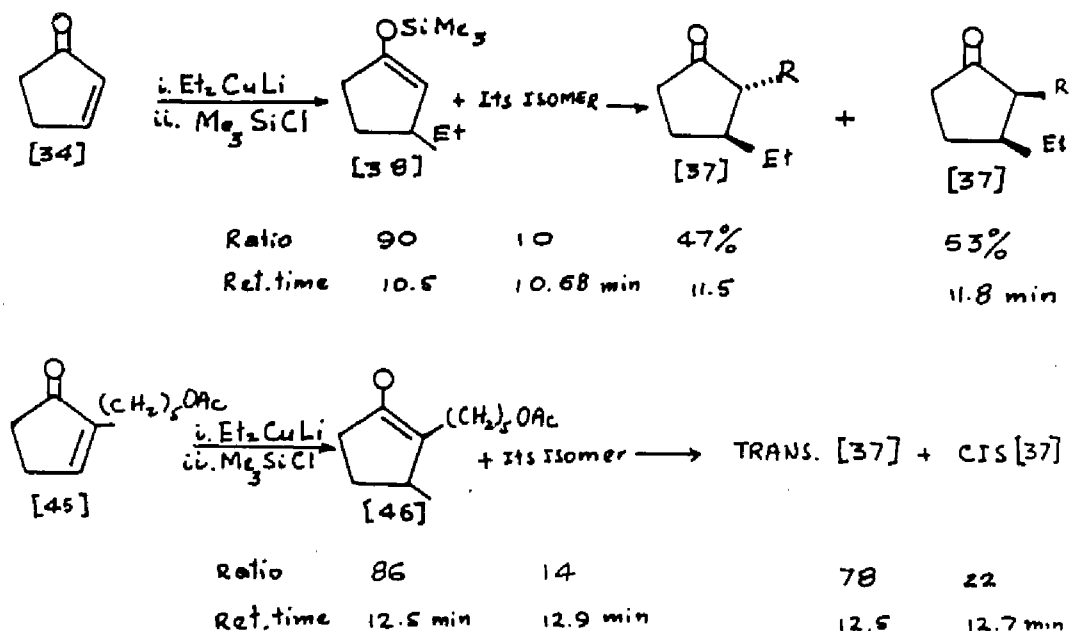


since the SiMe_2Ph group has roughly the same lability profile toward acids and bases as the $\text{Me}_2\text{Si}-$ group. However, using TLC on silica gel, eluting with 20% ethyl

acetate/hexane, [46] was converted to [37] with a cis:trans ratio 16:84. [46] which appeared to be a mixture of two isomers with a 86:14 ratio was hydrolyzed to [37] by either one of the following methods: i. treatment of [46] in a mixture of AcOH-H₂O-THF, ii. same as above but followed by refluxing with Et₃N. The latter is the least favored method because it gives [37] in 20% yield, compared to 50% yield in the former method.

Compare the alkylation of silyl enol ether [38], which gives somewhat more cis-[37] than trans-[37] (53:47 ratio), to the conjugation addition of organocuprate to [45],

Scheme 26.



which provides cis:trans [37] in 22:78 and 16:84 ratios. Obviously the latter reaction gives more stereospecific product than the former. This fact might be due to the nature of the intermediates [38] vs. [46]¹⁰⁷. The protonation of the enolate (after the alkylation of [38]), which affords [37], might be kinetically controlled. In contrast, the hydrolysis of [46] probably is thermodynamically controlled.

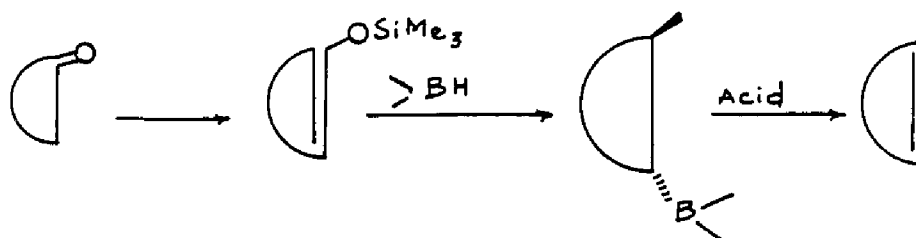
B. Conversion of ketone to olefin:

1. Introduction:

The reductive dehydration of ketones to form olefins has been accomplished in a variety of ways with generally only moderate success¹⁰⁸ such as the Shapiro¹⁰⁹ modification of the Bamford-Stevens reaction, the nickel reduction of a thioketal¹¹⁰, the lithium/amine reduction of N,N,N',N',-tetramethylphosphorodiamidates¹¹¹. Among the more recent and better ways to make this conversion are those involving hydroboration or hydroalumination of a functional olefin derived from the ketone. Thus, olefins have been prepared from the hydroboration of enamines¹¹² or enol acetates¹¹³ when the intermediate organoborane is treated with acid or via the hydroalumination of enamines¹¹⁴ or enol ether¹¹⁵ where the elimination

occurs spontaneously. Larson and his research group have reported a synthesis of olefins via hydroboration of cyclic trimethylsilyl enol ethers according to the sequence in Scheme 27 below:

Scheme 27.



Larson's route is advantageous since silyl enol ethers can be generated under conditions of either kinetic or equilibrium control. Thus, a considerable regioselectivity of the olefin formation can be attained. Several methods among those listed above were examined for conversions of [37] to 3-(5-acetoxypentyl)-4-ethylcyclopentene. The results are reported below.

2. Conversion of [37] to 3-(5-acetoxypentyl)-4-ethylcyclopentene [20]:

In a search for appropriate reaction conditions for a conversion of cyclic ketones to alkenes, six experiments (from a to f) were done, and their results are reported here. The reactions were carried out under the following conditions:

a. The silyl enol ether of cyclohexanone as a model compound was reacted with AlH_3 (generated in situ by the

reaction of LiAlH_4 and AlCl_3 to give different outcomes depending on the reaction conditions (ratio of AlCl_3 to LiAlH_4 , reflux time and work-up procedure). The results are summarized in Table 1. This method is unsatisfactory under any of the conditions tried, since only low yields of cyclohexene were obtained.

Table 1

<u>Ratio of</u> <u>AlCl_3/LAH</u>	<u>Color of</u> <u>AlCl_3</u>	<u>Refluxing</u> <u>time</u>	<u>Gas</u>	<u>Work-up</u>	<u>Results:</u>
1:3	Yellow	48h	N_2	i.	i.
1:3	Black	47h	Ar	ii.	ii.
1:2.86	Yellow	20h	Ar	iii.	iii.

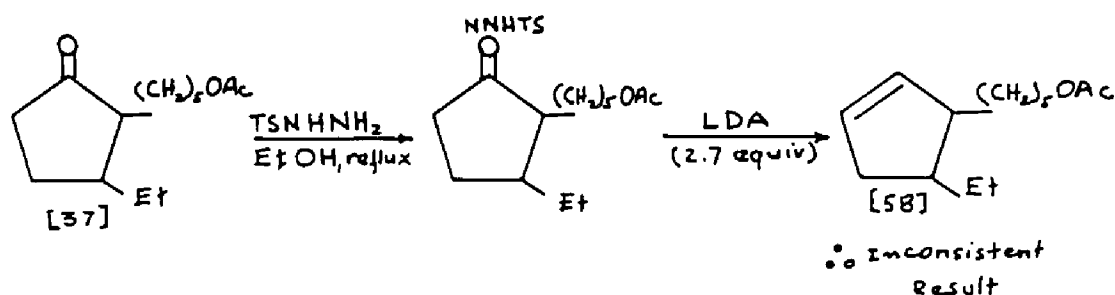
Work-up: i. 5M HCl. ii. 5M HCl; cold sat. NaHCO_3 .
iii. 0.5M HCl; cold sat. NaHCO_3 .

Results: i. Cyclohexanone (84%), dimer of cyclohexene (2%) [based on GC areas].
ii. Cyclohexanone (major) and cyclohexene (minor) [based on bp and a qualitative test for $\text{C}=\text{C}$].
iii. Cyclohexanone. Cyclohexene was not detected by ^1H NMR and MS.

b. The decomposition of sulfonylhydrazone salts is known to produce olefinic compounds via a carbenoid

mechanism, especially when carried out in an aprotic medium¹¹⁶. Use of this reaction for performing the conversion of ketoester [37] to the unsaturated compound appeared to be worth investigating, since carbonium ion intermediates would be avoided. The mixture of cis and trans ketoesters [37] was readily converted to a mixture of the corresponding toluenesulfonylhydrazones by treatment with toluenesulfonylhydrazine in ethanol at reflux for 3 h. Decomposition of the tosylhydrazone was carried out by adding it to 2.7 equivalents of LDA at -78°C for 10 min and stirring the reaction mixture at room temperature overnight. The results were not consistent over two runs. One run gave 14.3% of [58] based on GC. The another run afforded no [58] but gave 17 unidentified components which were derived from the unstable toluensulfonylhydrazone of [37] (GC/MS determined) (Scheme 28).

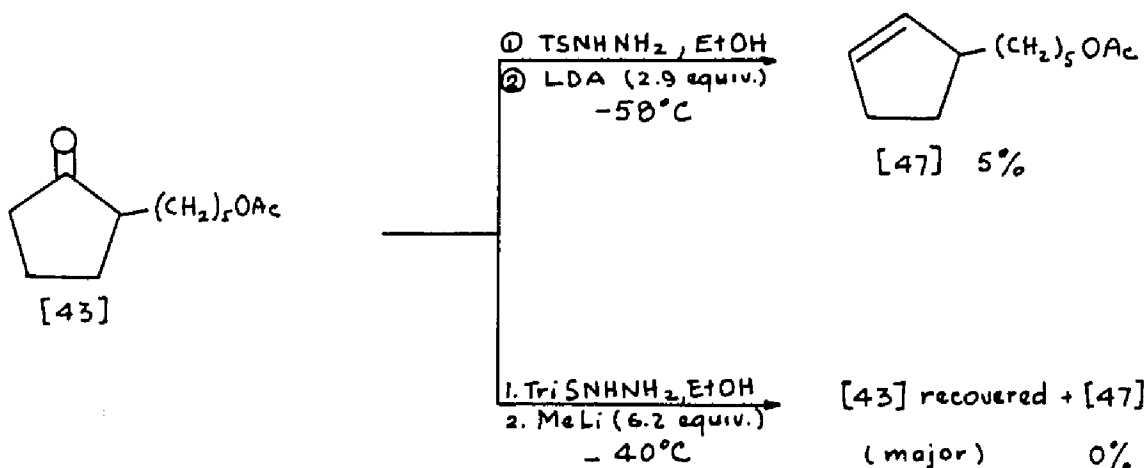
Scheme 28.



c. The Shapiro reaction as described above was also applied to 2-(5-acetoxypentyl)cyclopentanone [43]. The tosylhydrazone of [43] (prepared as in part b)

was reacted with 2.9 equivalents of LDA at -58°C over 10 min. The light yellow reaction mixture was warmed to room temperature (23°C), stirred at 23°C for 5 h., and worked up. According to GC/MS 5% of 3-(5-acetoxypentyl)cyclopentene [47] was obtained. In another case, triisopropylbenzenesulfonylhydrazine instead of toluenesulfonylhydrazine was used in a conversion of [43] to its corresponding hydrazone, which was treated with MeLi (6.2 equivalents) at -40°C for 5 min. After warming to room temperature (RT), the light yellow suspension was stirred at RT for 7.5 h and worked up. No product [47] was obtained based on ^1H NMR and MS analyses. The starting material [43] (major) along with ten unidentified components (minor) were obtained. (Scheme 29).

Scheme 29.



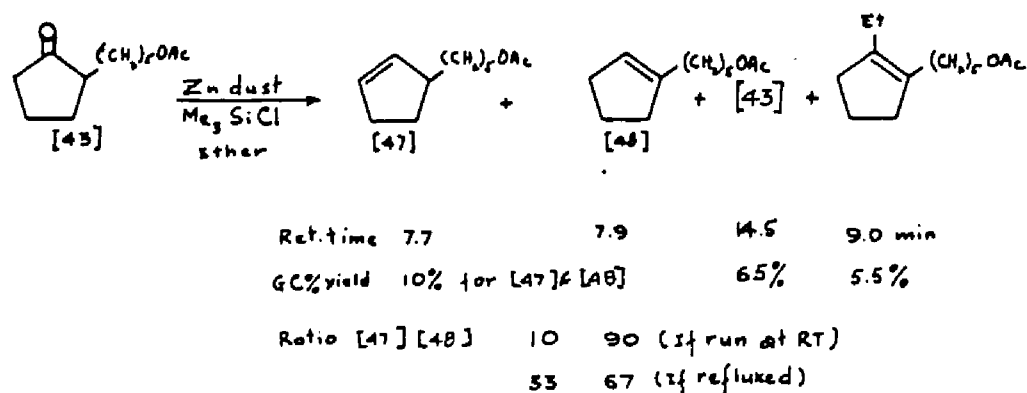
Thus the decomposition of sulfonylhydrazone salts is not useful to produce the olefinic compounds from 2-(5-acetoxypentyl)-3-ethylcyclopentenone [37] and 2-(5-acetoxypentyl)cyclopentanone [43] systems.

d. Motherwell^{108b} has reported that a convenient method for synthesis of olefins is the reaction of alicyclic ketones with Me_3SiCl and Zn in ether solution. The report has revealed that preparatively useful yields can be obtained under exceptionally mild conditions. In particular, the successful conversion of the functionalized cyclohexanones (bromo, acetoxy) highlights the selective nature of the process. Moreover, the reaction is easily carried out in a single reaction vessel, and thus is much more convenient than existing methods^{108a} including the Shapiro reaction.¹⁰⁹

The keto ester [43] (1 equiv) in ether was added to a rapidly stirred suspension of Zn (10 equiv) in dry ether containing Me_3SiCl (5 equiv) at room temperature for 12 days. The reaction led to 65% of starting material, 10% of a mixture of [47] and [48] (ratio 10:90) and surprisingly, 6% of 2-(5-acetoxypentyl)ethylcyclopentene [49] were obtained (based on GC, MS, and ^1H NMR analyses). The structural assignment of [47] and [48] was based on their ^1H -NMR spectrum which showed 2 vinylic hydrogen

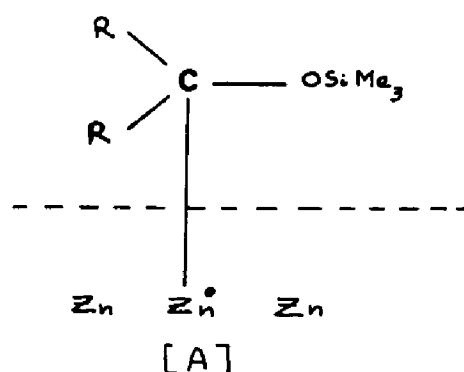
signals at 5.69 and 5.39, respectively. [49] was tentatively identified by its MS fragmentation pattern. The ethyl group in [49] perhaps was derived from a cleavage of ether in the reaction medium. In a similar experiment, the keto ester [43] was refluxed with Zn (10 equiv) and Me_3SiCl (10 equiv) to afford 61% of a mixture of [47] and [48] (ratio 33:67 respectively, determined by GC areas)(Scheme 30). Thus, unfortunately, the conditions required to achieve reasonable conversions led to lowered regiospecificity.

Scheme 30.



According to Hodge and Khan, the mechanism¹¹⁷ of the deoxygenation reaction is probably closely related to that of the Clemenson reduction. It proceeds through a very bulky intermediate such as [A]. This may be formed via the radical anion of the ketone and may react further to give a carbenoid^{108b} which inserts into a neighboring

C-H bond to yield an olefin. Some evidence supporting the carbenoid intermediacy are: i. the isolation of bicyclo-[3,3,0]octane from the reaction with cyclooctanone, ii. a similar type of carbenoid species has also been proposed in the reaction of benzaldehyde with BF_3 and Zn^{119} , iii. the mechanism is also consistent with the observed regio-

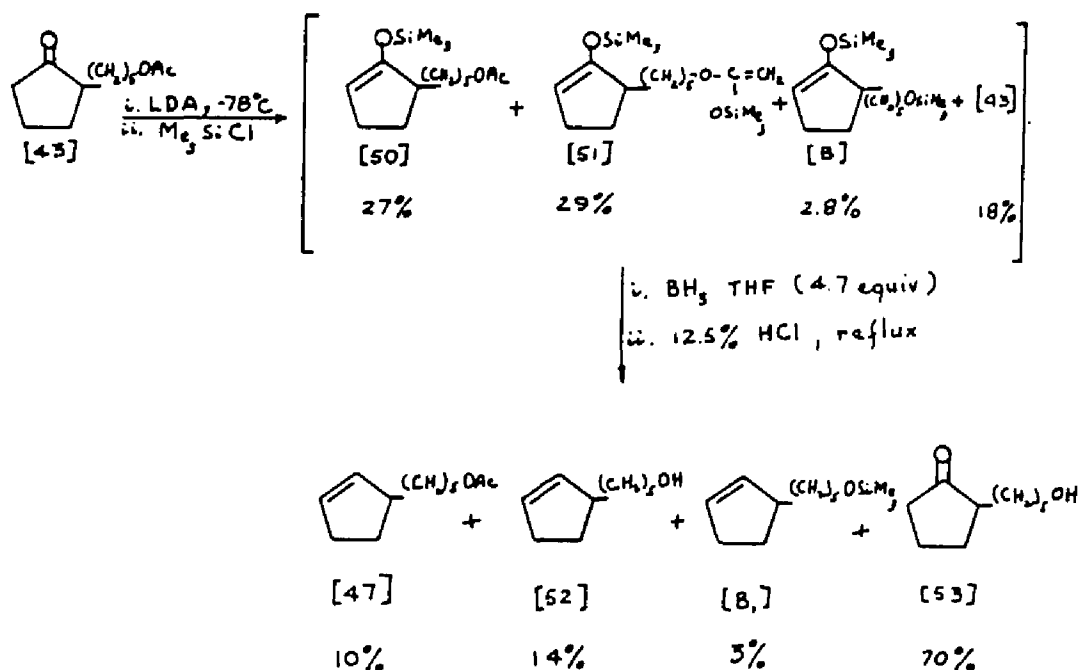


selectivity in the case of 2-methylcyclohexanone^{108b} (methyl cyclohexene and 3-methylcyclohexene in a 3.3 : 1 ratio) and [43] ([48] and [47] formed in a 9 : 1 ratio if run at room temperature and in a 2 : 1 ratio if refluxed).

e. The hydroboration of trimethylsilyl enol ethers occurs to place the boron atom on the β -carbon of the double bond^{119b}. In acyclic systems the resulting β -trimethylsiloxyorganoborane is not stable, undergoing a rapid elimination to form olefin, which is then hydroborated.^{119b, 120} However, the trans- β -trimethylsiloxyorganoboranes that result from the hydroboration

of cyclic trimethylsilyl enol ethers are much more stable and are converted to cyclic olefins upon treatment with an acidic catalyst. There are a variety of acids which catalyze the elimination reaction, including carboxylic acids, BF_3 ethyl etherate or simply aqueous HCl . Aqueous HCl is used as the most convenient. Following Larson's method¹¹⁹ to synthesize an olefin from a cyclic ketone, the keto ester [43] (1 equiv) was converted to the silyl enol ether under kinetic conditions by treatment with LDA (6.5 equiv) at -78°C and Me_3SiCl (10.8 equiv). A mixture of [50], [51], [B] and [43] (in the ratio: 27%, 29%, 3% and 18%, respectively, based on GC areas) was formed, treated with $\text{BH}_3\cdot\text{THF}$ (4.78 equiv) then with aqueous HCl , and refluxed for 4 h.

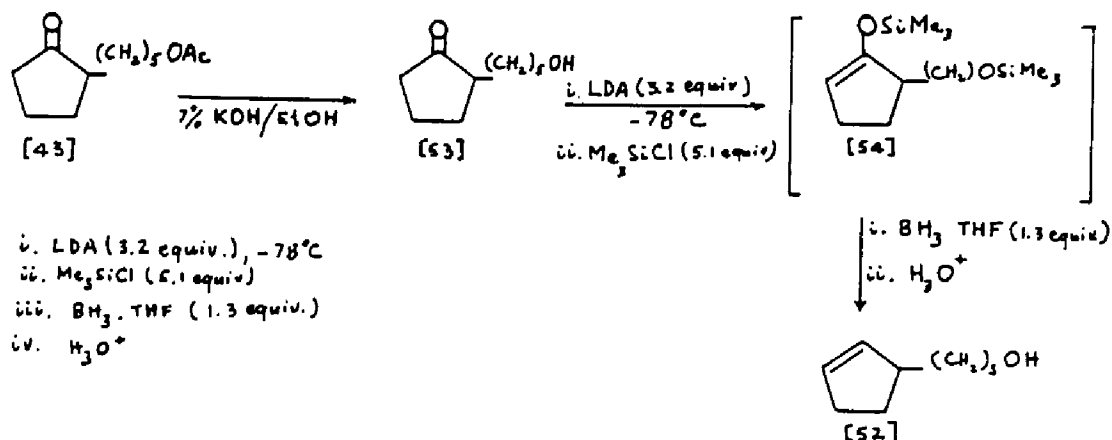
Scheme 31.



The resulting crude product consisted of [47], [52], [B'] and [53] (ratio: 10%, 14%, 3% and 70% respectively, by GC) and was preparatively chromatographed to produce a mixture of [47] and [52] (23% yield if calculated by MW of [52] and 29% yield by MW of [47]) (Scheme 31 above).

f. The presence of the ester function in [43] makes the silyl enol ether and product formation more complex as seen above. The problem can be avoided by converting the keto ester [43] to keto alcohol [53]. Hydrolysis of [43] with 7% methanolic KOH gave [53] in 74% yield. The reaction of [53] with LDA (3.2 equiv) at -78°C was followed by quenching of the anion with Me_3SiCl (5.1 equiv) to provide exclusively the unstable silyl enol ether [54]. Hydroboration of [54] with borane in THF (1.3 equiv) was

Scheme 32.

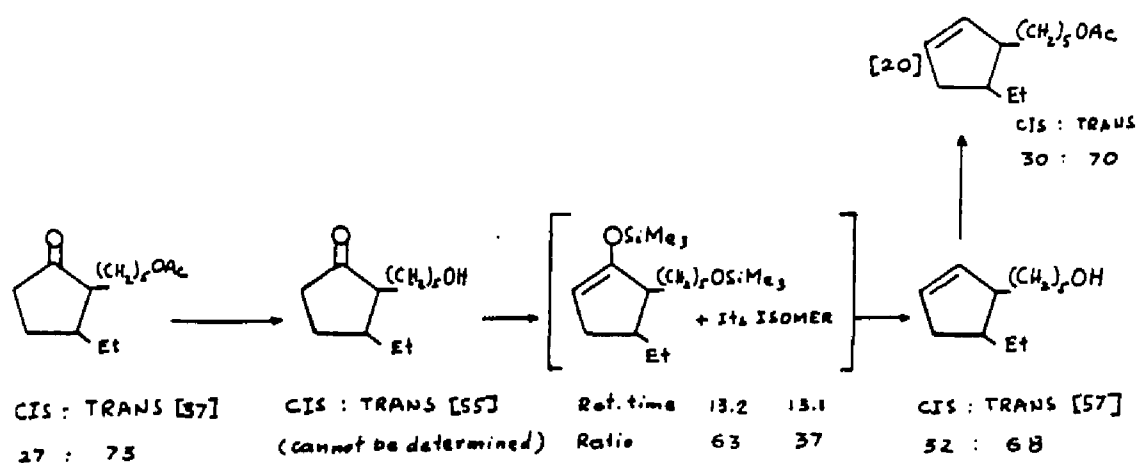


followed by elimination from the resulting trimethylsiloxy organoborane in aqueous HCl. The reaction mixture was refluxed for 4 h to afford [52] in 44.2% GC yield (11.7% isolated yield). No attempts have been made to optimize the yield. It is noted that again the Shapiro reaction of the keto alcohol [53] with toluenesulfonylhydrazine in EtOH and with MeLi gave no [52]. Thus the synthesis of the olefin [52] via hydroboration of the silyl enol ether (Scheme 32) is the best method among the six listed experiments. The low yield for the keto alcohol [53] system can be attributed to the fact that the intermediate organoborane undergoes an elimination before the addition of the acid and that the resulting [52] is then hydroborated. It is noted that hydroboration elimination serves very well for those systems which are symmetrical and work well for those systems in which the trimethylsilyl enol ether could either be selectively prepared (kinetic or thermodynamic conditions) as seen above.

After six initial attempts had been examined and the best conditions for the conversion chosen, the synthesis of [57] from [37] was carried out by the sequence of steps in Scheme 33. The keto alcohol [55] (1 equiv) was formed in 86% yield (cis/trans = 27/73 by GC) by treatment of [37] with 7% ethanolic KOH at room temperature for 24 h. [55] was then reacted with LDA (2.05 equiv) at -78°C and quenched with Me_3SiCl (3.45 equiv) to give a mixture of

unstable silyl enol ether [56] and its positional isomer (retention time 13.1 and 13.2 min), ratio 37:63, respectively). The mixture [56] was hydroborated by $\text{BH}_3 \cdot \text{THF}$ (1.75 equiv), followed by treatment with aqueous HCl under reflux for 4 h. The 3-(5-hydroxypentyl)-4-ethylcyclo-

Scheme 33.

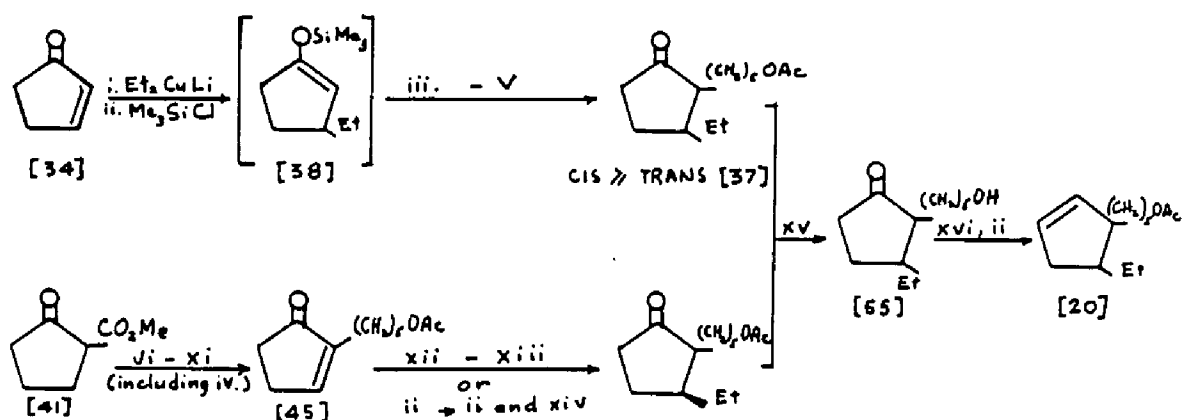


pent-2-ene [57] was obtained from [55] in 63% yield (cis:trans = 32:68 based on ^1H NMR, 400 MHz). Acetylation of [57] in acetic anhydride and pyridine afforded 3-(5-acetoxypentyl)-4-ethylcyclopentene in 99% yield (cis:trans = 30:70 based on ^1H NMR, 400 MHz).

3. Summary of Routes to [20]: The syntheses of [20] from 2-cyclopentenone (Route A) and 2-carbomethoxycyclopentanone (Route B) are summarized in Scheme 34. In route A, Et_2CuLi was conjugatively-added to 2-cyclo-

tenone, and the resulting enolate was trapped with Me_3SiCl to provide the intermediate [38] in 65% yield. The lithium enolate was generated regiospecifically from [38] with LiNH_2 in $\text{NH}_3\text{-THF}$ and then alkylated with [40] to produce a 53:47 ratio of the cis and trans isomer [37] in 41% yield (optimized). [37] was also prepared from 2-

Scheme 34.



iii . Li , NH_3 ; iv. $\text{Br}(\text{CH}_2)_5\text{OAc}$; v. NH_4Cl ;

vi . K_2CO_3 / Acetone then iv; vii. $\text{AcOH}/25\% \text{HCl}$;

viii. CaCO_3 / CHCl_3 . Br_2 / CCl_4 ;

ix . Li_2CO_3 , LiBr , DMF ; x. EtMgBr-CuI then v;

xi . $\text{AcOH-THF-H}_2\text{O}$; xii. $7\% \text{KOH/EtOH}$; xiii. LDA , -78°C

xiv . $\text{BH}_3\text{-THF}$; xv. aq.HCl ; xvi. Ac_2O , pyridine.

carbomethoxycyclopentanone [41] (Route B) by the follow-

ing sequence of 6 steps: i. the alkylation of [41] with [40] in the presence of K_2CO_3 /acetone afforded [42] in 77% yield. ii. the hydrolysis and decarboxylation of [42] were carried out by refluxing in aqueous acid ($AcOH/25\% HCl$) to give [43] in 75% yield. iii. the conversion of [43] to [45] was accomplished by halogenation of enol acetate [44], and subsequent dehydrohalogenation. Enol acetylation of [43] with refluxing acetic anhydride and p-toluenesulfonic acid catalyst provided [44] in 58% yield. Bromination of [44] was done in a three phase reaction medium ($CaCO_3/CHCl_3$ and Br_2/CCl_4) to produce bromoketones, which were treated with the $LiBr/Li_2CO_3$ in DMF to form [45] in 52% yield from [44]. The conjugate addition of the ethyl group at the β -carbon atom of [45] was performed by using either Et_2CuLi in the presence of Me_3SiCl or $EtMgBr-CuI$, and followed by the hydrolysis of the intermediates of the conjugate addition reaction. The best yield (50% without optimization) of [37] with more trans than cis isomer (ratio 78:22) was obtained with Et_2CuLi . The overall yield for the formation of [37] from 2-carbomethoxycyclopentanone (Route B) was 8.7%, compared to 26.7% from 2-cyclopentenone. The more steps (6 steps) caused the lower yield of [37] in route B. However, route B gave more stereospecific product [37] than route A to compensate the lower yield. The ketoester [37] was converted to the corresponding silyl enol ether [56] via

the keto alcohol [55], which was hydroborated. Then the intermediate of the hydroboration reaction underwent a regiospecific elimination on treatment with aqueous HCl to yield the specific alkene [57]. The preparation of [20] (cis:trans isomer in a 30:70 ratio) was accomplished with acetylation of [57] in the presence of acetic anhydride and pyridine as described above. The overall yield of [20] from [37] was 55% .

C. Conversion of ketones to alkanes :

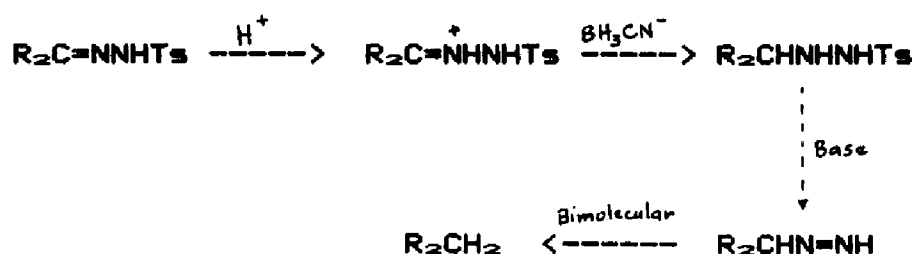
1. Introduction:

There are various ways of reducing the C=O group of ketones to -CH₂-¹²¹. The two most important methods are the Clemmensen reduction, consisting of heating the ketone with Zn amalgam and aqueous HCl¹²², and the Wolff-Kishner reduction¹²³, in which the ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The Huang-Milon modification¹²⁴ of the Wolff-Kishner reaction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. The Clemmensen and Wolff-Kishner reactions are complementary, since the former uses acidic and the latter basic conditions. However, the standard procedures are often afflicted with problems. In particular, the rather vigorous conditions and harsh reagents required for most methods preclude the presence of many other susceptible functional groups. For example, the use of strong base and high temperatures in the standard Wolff-Kishner modification introduced by Caglioti¹²⁵, which involves NaBH₄ reduction of ketone tosylhydrazones, is a much milder procedure. Nevertheless, the selectivity of borohydride is not high at the reduction temperatures (refluxing methanol or dioxane). For instance, concomitant reduction of acetoxy groups was observed by Caglioti¹¹³ and

reduction of esters by borohydride has been observed by others¹²⁶.

Hutchins and his research group¹²⁷ have reported that the reduction of aliphatic ketone tosylhydrazones with sodium cyanoborohydride in acidic 1:1 DMF-sulfolane and cyclohexane provides a mild, convenient, and high-yield method for deoxygenation without the production of side products. A noteworthy feature and advantage of the procedure is superior selectivity, in that most other functional groups (i.e. ester) are not affected under the reaction conditions, allowing carbonyls to be removed in their presence. Scheme 35 below illustrates the envisioned reaction path in line with the postulated mechanism for borohydride reduction of tosylhydrazones^{125, 128} and the known decomposition pathway of diazenes¹²⁹.

Scheme 35.

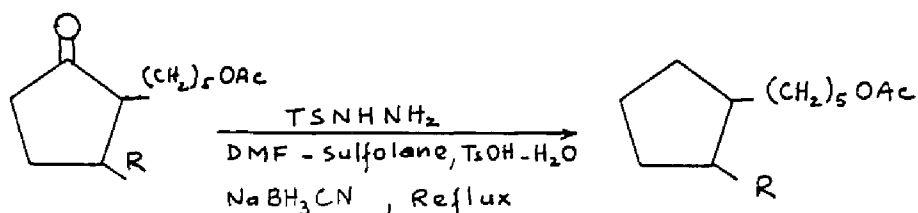


The yield of hydrocarbon product varied considerably with solvent, the most favorable medium employed was a 1:1 mixture of DMF and sulfolane. Several others such as sulfolane, DMF, HMPA, DMSO, dioxane, methanol, and

2-propanol gave less satisfactory results¹²⁷. The cyclohexane solution in the reaction mixture serves two purposes¹²⁷. First, the immiscibility with DMF and sulfolane allows the hydrocarbon product to be removed from the solvents as it is formed, this minimizes contact of other functional groups with the reducing system. Secondly, the blanket of cyclohexane vapor prevents the destruction of the intermediate diazenes by oxygen¹⁴⁰, in fact, if the reactions are run in the presence of oxygen, the yields of products are greatly reduced.

2. Conversion of [37] to 2-(5-acetoxypenty)-1-ethyl cyclopentane [18]:

Hutchins' method was examined with the model compound [43] before applying it to [37]. The ketoester [43] (1 mmol) and *p*-toluenesulfonylhydrazine (1.25 mmol) were dissolved in 5 mL of 1:1 DMF-sulfolane containing 25 mg of *p*-toluenesulfonic acid monohydrate. The solution was heated to 100 to 105°C and NaBH₃CN (4 mmol) then 5 mL of cyclohexane added. The reaction mixture was refluxed for 6 h to furnish [59] and starting material [43] (53.8% and 38.9%, respectively, based on GC). (Scheme 36).

Scheme 36.

[43] R = H

[59] R = H

[37] R = Et

[18] R = Et

In a similar manner, [37] (cis/trans = 27/73) was treated with *p*-toluenesulfonylhydrazine in DMF-sulfolane having *p*-toluenesulfonic acid monohydrate as a catalyst, and NaBH₃CN to give [18] and starting material [37] (19% and 81%, respectively, determined by GC). The stereochemistry of [18] has not been determined (see stereochemical assignment section below).

The low yield of products may be due to several factors. Tosylhydrazone formation in DMF-sulfolane was extremely slow and varying amounts of the ketones were recovered unchanged even after several hours at 100 to 105°C. The reductions of the tosylhydrazones in acidic DMF-sulfolane were also slow. The acid concentration is an important factor, as Hutchins¹²⁷ reported. Increasing the acid concentration markedly accelerates

the reduction rate. However, at pH lower than ca. 1, destruction of cyanoborohydride apparently competes with reduction, resulting in lower final yields of hydrocarbon products.

III. RESULTS AND DISCUSSION OF 6-MEMBERED RING SYSTEMS:

A. Introduction:

As mentioned earlier in the introduction part of the results and discussion, this chapter intends to review preparation of some α, β -dialkylcyclohexanones.

1. Review of preparation of α, β -dialkylcyclohexanones:

a. General strategy:

The search for a proper starting material in the synthesis of α, β -dialkylcyclohexanones involves the same problems discussed earlier with respect to 2,3-disubstituted cyclopentanone syntheses. Cyclohexanone is not a suitable precursor for the same reasons presented in the case of cyclopentanone. Similarly, 2-cyclohexenone, 2-alkylcyclohex-2-enones, and 2,3-dialkylcyclohex-2-enones would be suitable starting materials. The 3-alkylcyclohex-2-enones and 3-alkyl-2-carbalkoxycyclohexanones are additional possibilities. 2-cyclohexenone, 2-alkylcyclohex-2-enone and 2,3-dialkylcyclohex-2-enone are converted to α, β -dialkylcyclohexanones by conjugate addition-alkylation, conjugate addition, and hydroge-

nation of -C=C- bond, respectively. Reduction-alkylation or vice versa, and alkylation-decarboxylation are applied for conversions of 3-alkylcyclohex-2-enones and 3-alkyl-2-carbalkoxycyclohexanones to α, β -dialkylcyclohexanones, respectively.

In general, trans-2,3-dialkylcyclohexanones are formed predominantly over the cis-isomer in all reactions noted above except in the hydrogenations of α, β -dialkylcyclohexanones which has the potential for giving mainly cis-product. The actual stereochemical course of the hydrogenation reaction is influenced by the nature of solvents and by the presence of acid or base in the reaction mixture¹³⁰, therefore, it is often difficult to predict the stereochemistry of the products. The detailed stereochemistry of the 2,3-dialkylcyclohexanones in each conversion will be discussed later.

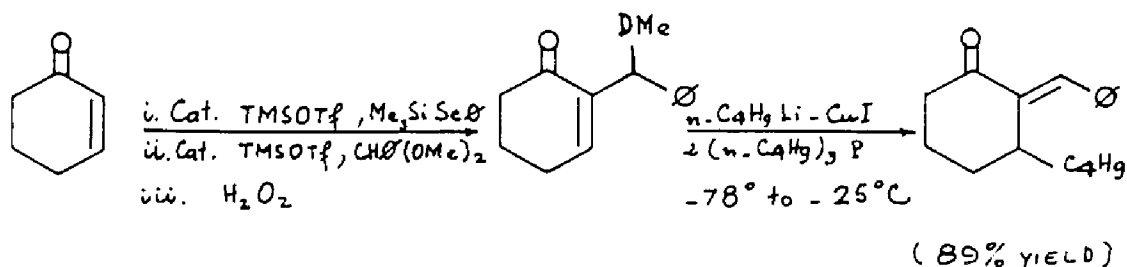
b. Classification of syntheses:

2,3-dialkylcyclohexanone syntheses may be divided into 4 major classes: i. syntheses in which 2-alkylcyclohex-2-enones are the precursors, ii. syntheses which commence either from 3-alkylcyclohex-2-enones or 3-alkyl-2-carbalkoxycyclohexanones, iii. syntheses in which 2-alkylcyclohex-2-enones are used as the starting materials. iv. syntheses in which 2,3-dialkylcyclohex-2-en-1-ones are the forerunners.

2. Cyclohex-2-enone precursor: conjugate addition alkylation approaches:

Most methods which were described in the previous chapter involving a 2-cyclopentenone precursor could be applied using 2-cyclohexenone. Noyori's method⁶⁰ which was based on combination of α -alkoxy-alkylation of α, β -unsaturated ketones in one pot with the organocopper conjugate addition reaction has also been used in the preparation of 2,3-dialkylcyclohexanones. A typical example is illustrated by Scheme 37.

Scheme 37.

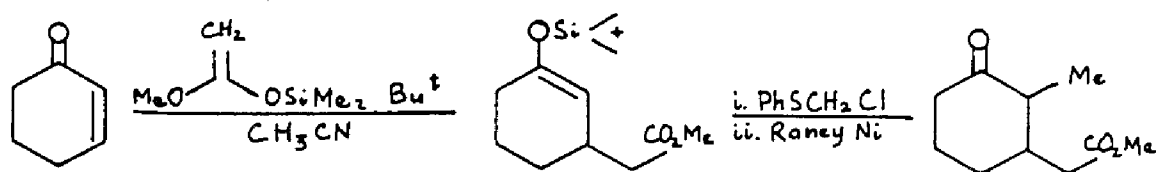


The Noyori method is characterized by initial carbon-carbon bond formation at the α -position of enones, which avoids formation of α, β -condensation products.

Tamura and his co-workers⁶¹ found that the O-di-methyl-t-butylsilyl enolate was obtained from 2-cyclohexenone and ketene silyl acetals in acetonitrile, and could be alkylated with α -chloromethyl phenyl sulfide in the presence of TiCl_4 . Desulfurization of the product with Raney nickel gave methyl(2-methyl-3-oxo-cyclohexyl)acet-

ate. This vicinal dialkylation of 2-cyclohexenone via the enolate had been applied in the simple route to α, β -di-alkylcyclopentanones from 2-cyclopentenone already seen before (Scheme 3B). The reason why Tamura's group did not simply alkylate the O-dimethyl-t-butylsilyl enolate with

Scheme 3B.

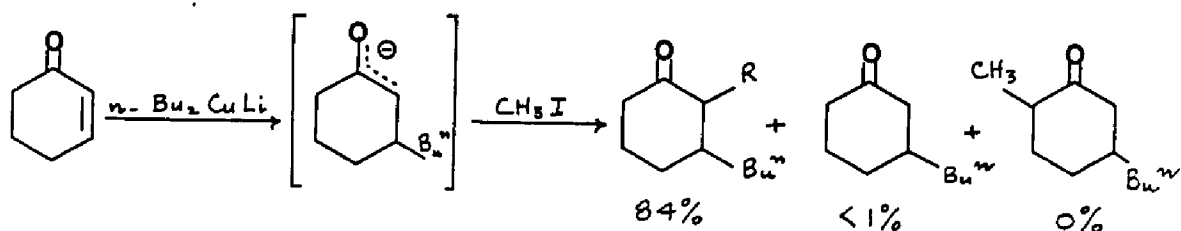


MeI was not reported. However, Weber^{40c} has noted that enolate anions react readily with primary alkyl halides by S_N2 displacement reaction while trimethylsilyl enol ethers only react easily with benzylic, allylic and tertiary alkyl halides. The use of α -chloroalkyl phenyl sulfides may overcome the reactivity limitation of trimethylsilyl enol ethers. α -Chloroalkyl phenyl sulfide reacts with trimethylsilyl enol ethers in the presence of TiCl₄ or ZnBr₂ to yield α -(α' -phenylthio alkyl) ketones whose oxidative sulfur removal provides the α -methylenketones. Alternatively, sulfur can be removed reductively by Raney nickel hydrogenolysis to make available a new method for the regiospecific α -methylation of ketones. The method is therefore a useful addi-

tion to the other methods of silyl enol ether methylation, namely formation of the directed lithium enolate and alkylation with methyl iodide. The attractive features of the reaction in which the *O*-dimethyl-*t*-butylsilyl enolate was formed are that: i. the use of acetonitrile as a solvent can greatly enhance the reactivity of the acetal toward the enone without catalyst to give almost quantitative yield of the silyl enolate; ii. the enolate which is obtained from the enone directly can be used to introduce the α -substituent readily.

Posner has described a procedure²⁴ in which 2-cyclohexenone reacts with excess lithium dibutylcuprate in THF at -78°C for 30 min to produce the corresponding enolate ion. Addition of excess MeI in HMPA at -78°C and warming to between -40 and -30°C (but no higher) gave trans- and cis-3-butyl-2-methylcyclohexanone in 7:1 ratio in 84% yield. One limitation of this method was encountered. The preservation of enolate regioselectivity during alkylation requires that the rate of alkylation be significantly greater than proton transfer^{25a}. With very reactive electrophiles such as benzylic and allylic halides, alkylation is significantly more rapid than proton exchange, and regioselective vicinal alkylation results^{26, 27b, c}. (Scheme 39).

Scheme 39.



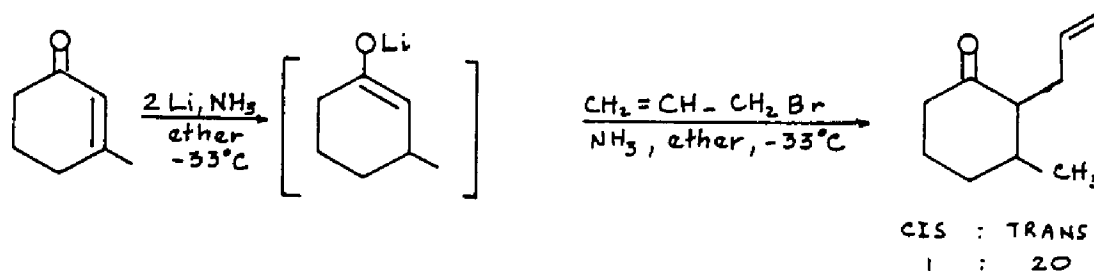
3. 3-Alkyl-2-cyclohexenone or 3-alkyl-2-carbalkoxy-
cyclohexanone precursors: reduction- alkylation
or alkylation-decarboxylation approaches:

The reduction-alkylation procedure developed by Stork and co-workers¹³⁰ often provides an excellent method for directing alkylation to relatively inaccessible α -positions of unsymmetrical ketones, and it has been applied successfully in a number of decalin, hydrindanone, and steroid systems. In general terms, the procedure involves:

- i. generation of a specific lithium enolate of an unsymmetrical ketone by reduction of the corresponding α, β -unsaturated ketone with 2 equivalents of Li in liquid NH_3 and
- ii. reaction of this enolate with an alkylating agent either in liquid NH_3 or other solvent system.

Caine and Chao¹³² have adapted Stork's method to the preparation of 2-allyl-3-methylcyclohexanone as a 20:1 mixture of trans- and cis-isomers in 54-66% yield (Scheme 40). Again the

Scheme 40.

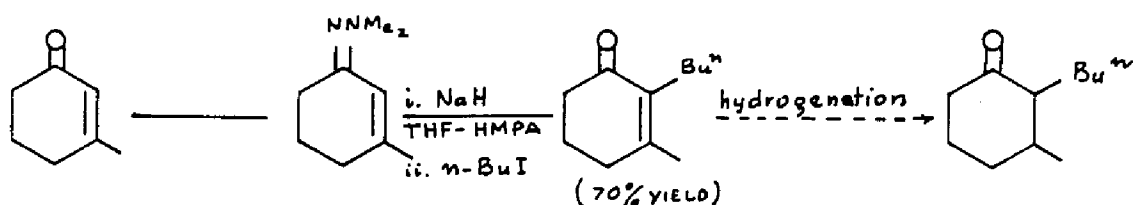


success of the method depends upon the now well-established fact that alkylation of specific Li enolates of unsymmetrical ketones with relatively reactive alkylating agents occurs faster in a variety of solvents than does equilibration among the structurally isomeric enolates via proton-transfer reactions.

It should be noted that alkylation of 3-methyl-2-cyclohexenone in ether using sodium amide or sodium hydride and in *t*-butyl alcohol containing potassium *t*-butoxide failed¹²².

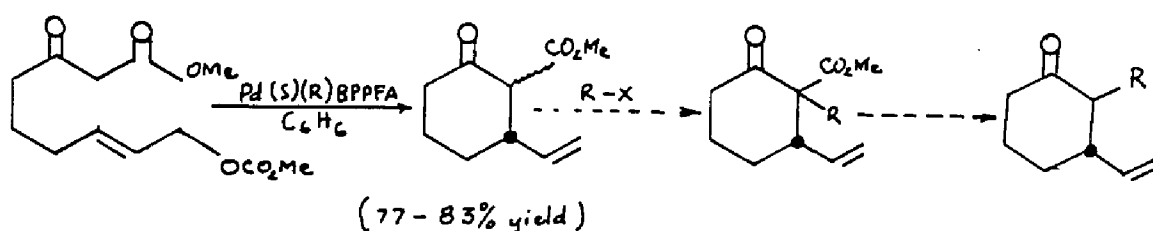
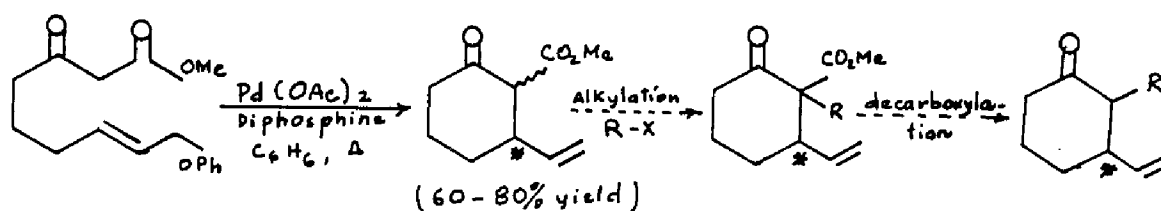
Stork and Behain¹²⁴ have reported that simple α, β -unsaturated ketones can be monoalkylated by making use of the metalloenamines derived from the treatment of the corresponding *N*-alkylimines with strong bases (Scheme 41).

Scheme 41.



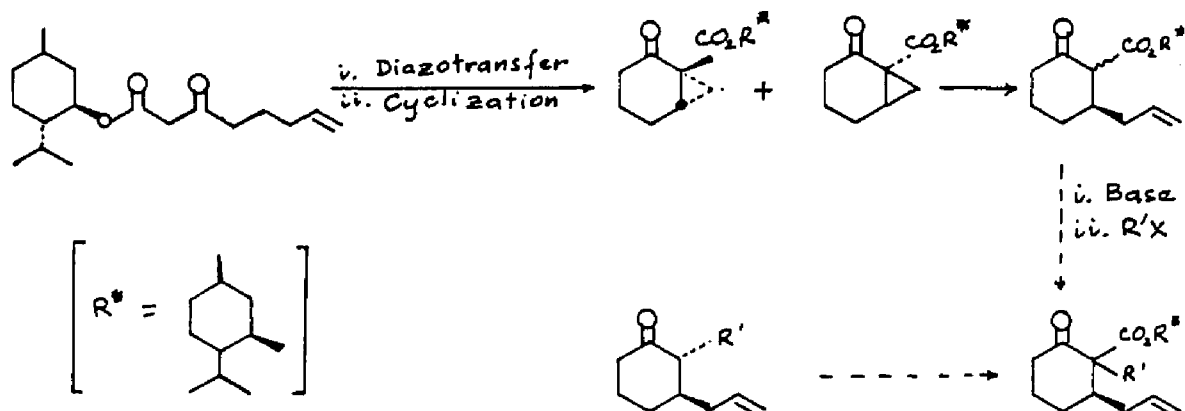
The relatively slow proton transfer with imines, coupled with the reluctance of enamines (and of metalloenamines) toward dialkylation, allows the success of this monoalkylation.

3-Alkyl-2-carbalkoxycyclohexanones, which can be used in 2,3-dialkylcyclohexanone syntheses by alkylation and decarboxylation, are prepared by Yamamoto's¹³⁵ and Taber's method¹³⁶. These methods also aim at eventual preparation of 2,3-disubstituted cyclopentanones. Yamamoto and Tsuji¹³⁵ have found that asymmetric cyclizations of (E)-3-oxo-9-phenoxy-7-nonenoate or methyl (E)-3-oxo-9-(methoxycarbonyl)oxy-7-nonenoate without added base can be carried out in the presence of a catalytic amount of Pd(II) acetate and a chiral diphosphine ligand to form the corresponding 3-alkyl-2-carbalkoxycyclohexanone. (Scheme 42)

Scheme 42.

[BPPFA = N,N-dimethyl-1-1',2-bis(diphenylphosphino)ferrocenyl] ethylamine]

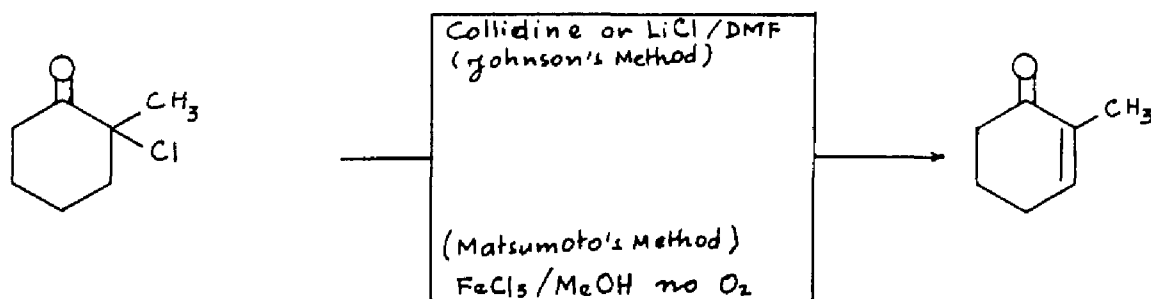
Taber and his researchers¹⁴⁷ have devised a general method for the preparation of alkylated cyclohexanones (also for cyclopentanones) of high optical purity. The important step is the diazo insertion-homoconjugate addition route. This offers the advantage that an early, flexible intermediate, the cyclopropyl ketone, incorporates the key β -asymmetric center and so is a candidate for resolution. Another advantage of this approach is that an optically pure resolving agent can be incorporated directly. (Scheme 43).

Scheme 43.

4. 2-alkyl-2-cyclohexenone precursors: conjugate addition approaches:

2-Alkyl-2-cyclohexenones can undergo conjugate addition of organometallic reagents to form α, β -dialkylcyclohexanones. The syntheses of the precursors are described below.

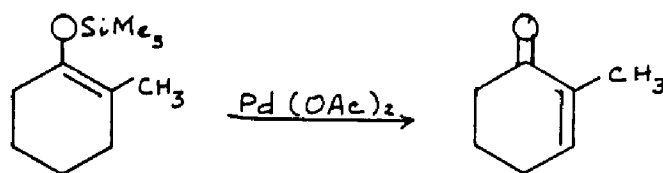
2-Methyl-2-cyclohexenone has been prepared from 2-chloro-2-methylcyclohexanone by dehydrochlorination with

Scheme 44.

collidine or LiCl in DMF (Johnson's method)¹³⁷ or FeCl₃ in methanol (Matsumoto's method)¹³⁸ (Scheme 44). It should be noted that in the presence of oxygen, Matsumoto's method yields adipic acid diesters from 2-chloro-2-methylcyclohexanone instead of the elimination product.

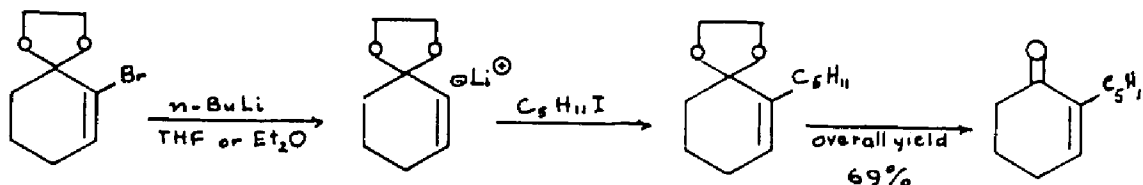
2-Methyl-2-cyclohexenone has also been prepared by Saegusa, Hirao, and Ito²⁵ from 2-methyl-1-trimethylsiloxy-cyclopentene via Pd(II)-catalyzed dehydrosilylation in 94% yield (Scheme 45).

Scheme 45.



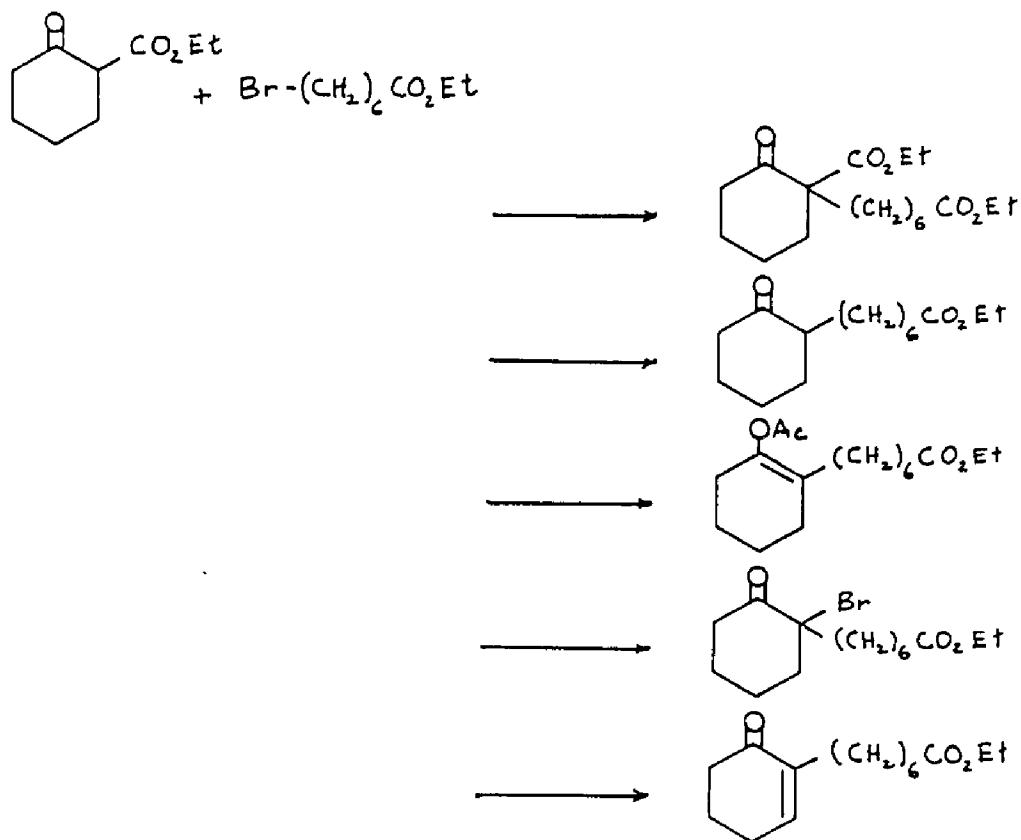
Smith and his co-workers¹³⁹ have reported an efficient method for the construction of a variety of α -substituted, α, β -unsaturated ketones directly from the parent enone by a method which does not require intervention of the thermodynamic dienolate (Scheme 46).

Scheme 46.



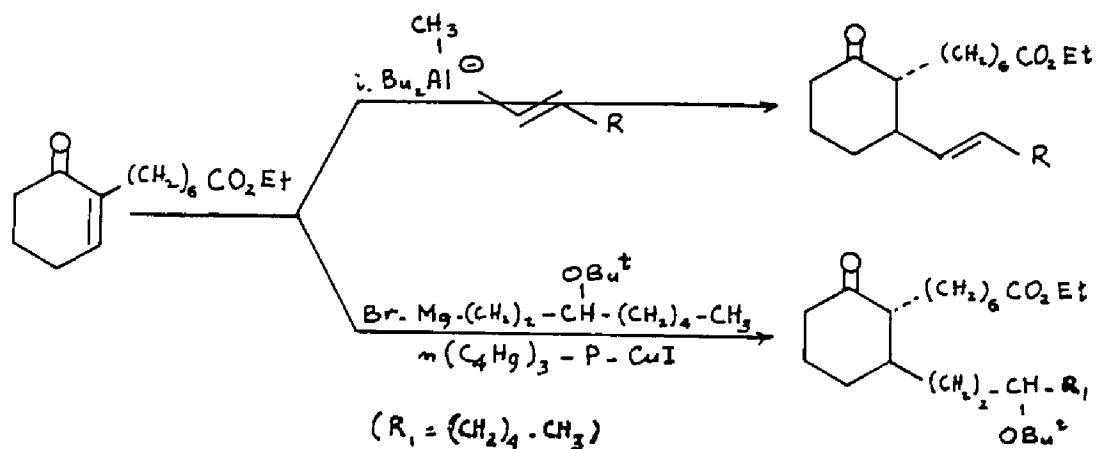
As with 2-alkyl-2-cyclopentenones¹⁴⁰, the corresponding cyclohexenones have been synthesized from 2-carbalkoxycyclohexanones and alkyl halides by the sequence: alkylation, decarboxylation, enol acetylation, bromination and dehydrobromination, as shown in Scheme 47.

Scheme 47.



The conjugate addition of lithium trialkyl-trans-1-alkenylalanates or Grignard reagents (in the presence of a catalytic amount of tributylphosphine-cuprous iodide complex) to the 2-alkyl-2-cyclopentenone in Scheme 48 gives the corresponding α, β -dialkylcyclohexanones.

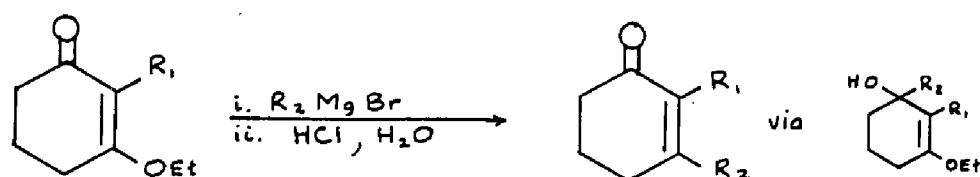
Scheme 48.



5. 2,3-dialkyl-2-cyclohexenone precursor: -C=C-
reduction approaches:

Approaches to 2,3-dialkylcyclohexanones from 2,3-dialkyl-2-cyclohexenones are carried out via the reduction of C=C. Thus it is necessary to review some 2,3-dialkyl-2-cyclohexenone syntheses from a variety of starting materials, such as: i. enol ether; ii. 3-alkyl-2-cyclohexenones; iii. 2,6-dialkyl-2,6-dicyanopiperidines; iv. and Hagemann'ester.

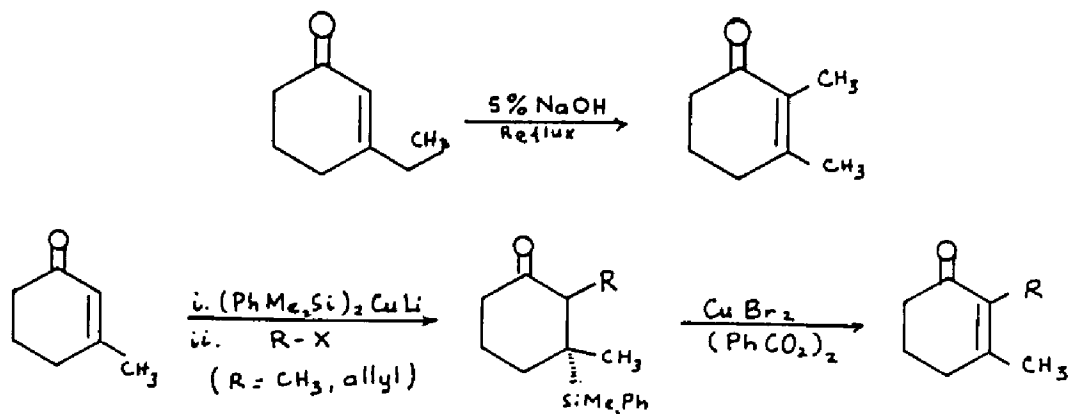
i. Enol ethers of the type shown in Scheme 49 react with Grignard reagents to afford unstable alcohols which are treated with 5% aqueous HCl at 25°C for 2 h to obtain α, β -disubstituted 2-cyclohexenones¹⁻⁴.

Scheme 49.

$R_1 = Me, n-C_5H_{11}$

$R_2 = -CH_2-CH(=CH_2)-(CH_2)_4-OTHP, n-C_{10}H_{21}$

ii. 3-Alkyl-2-cyclohexenones are converted to 2,3-di-alkyl-2-cyclohexenone by either refluxing¹⁴² for 3 h with 5% NaOH (retroaldol-aldol route) or conjugate addition/alkylation¹⁴³ (Scheme 50).

Scheme 50.

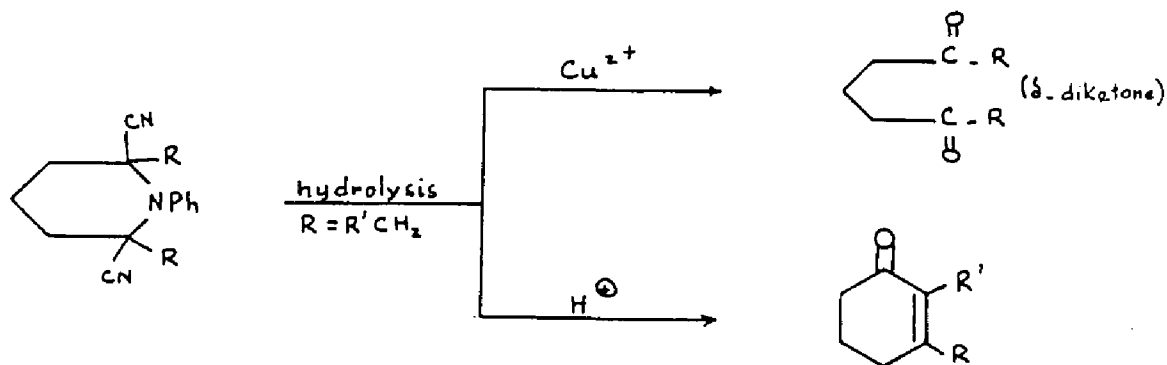
The lithium bis-[dimethyl(phenyl)silyl]cuprate [prepared from dimethyl(phenyl)silyllithium and copper iodide] adds to the β -position of the enone and generates the enolate,

which can be alkylated directly with methyl and allyl iodides (other simple primary alkyl iodides are too unreactive). A bromination of the ketone is then carried out in a mixture of benzoyl peroxide and copper (II) bromide, followed by desilylbromination of the β -silylketone to produce the 2,3-disubstituted 2-cyclohexenone in 60% overall yield. This method has also been used for a synthesis of a five-membered ring analog.

Compared to Me_2SiLi which has to be prepared from bis-(trimethylsilyl)mercury, $\text{PhMe}_2\text{SiLi}^{142}$ can be easily made from PhMe_2SiCl or 1,1,2,2-tetramethyl-1,2-diphenyldisilane using Li and can add to hindered enones, such as isophorone.

iii. Hydrolysis of 2,6-dialkyl-2,6-dicyanopiperidines in an aqueous solution of 15% HCl using THF as a cosolvent gives the corresponding α, β -unsaturated cyclohexanone¹⁴⁴ in high yields (62-100%) except for the case where R' is $\text{CH}_2=\text{CH}$ (Scheme 51). The 2,3-dialkyl-2-cyclo-

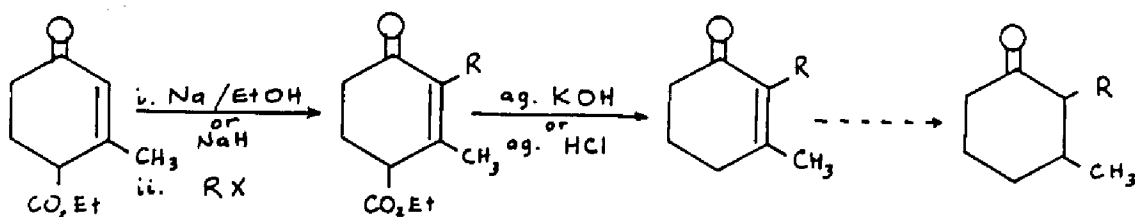
Scheme 51.



hexenones are obtained by intramolecular condensation of the δ -diketones, whose formation is noted in the initial period by means of thin-layer-chromatography. On the other hand, when the hydrolysis is carried out in an aqueous solution of cupric sulfate or cupric acetate containing dioxane or ethanol as a cosolvent, the δ -diketones are selectively obtained in good yields, and the formation of the 2-cyclohexenones is not detected at all.

iv. A preparation of α -alkyl- β -methylcyclohexanones¹⁴⁵ from commercially available Hagemann's ester by alkylation and decarboxylation is a simple method with a 2-step conversion, as shown below in Scheme 52.

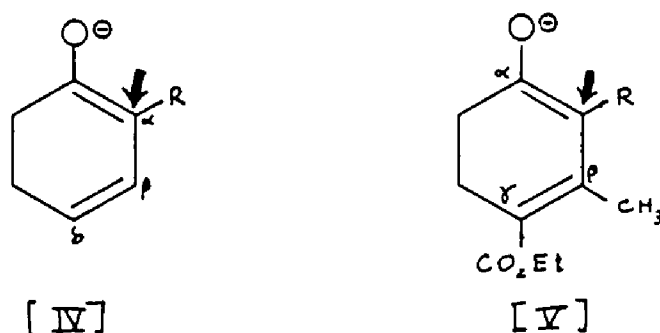
Scheme 52.



Previous studies^{145, 146} have shown that Hagemann's ester undergoes alkylation at the 3-position in ethanolic EtONa and in 1,2-dimethoxyethane or toluene using NaH to prepare the enolate. The alkylated Hagemann's ester was

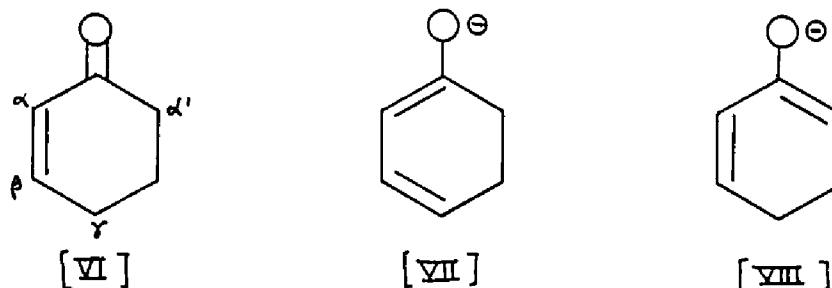
obtained in better yield under the latter condition (NaH in toluene). The NMR spectrum of the resulting product (see the Experimental Section) confirmed formation of the 3-substituted derivative by disappearance of the vinylic hydrogen peak near 6.0 ppm as reported earlier ^{145,146}. Paquette and his co-workers¹⁴⁷ have described that thermodynamic enolates, e.g., [IV] (Fig. 1) have a strong

Fig. 1.



tendency to undergo irreversible C-alkylation at their α -position, even when this site is substituted. The presence of an activating group as in Hagemann's ester [V] is not sufficient to overcome this tendency. Recently, Bartmess and Kiplinger¹⁴⁸ have been able to determine "kinetic" vs. "thermodynamic" acidities of 2-cyclohexenone [VI] in the gas phase (Fig. 2). In [VI] there are 2 sites for deprotonation by bases of reasonable strength:

Fig. 2.

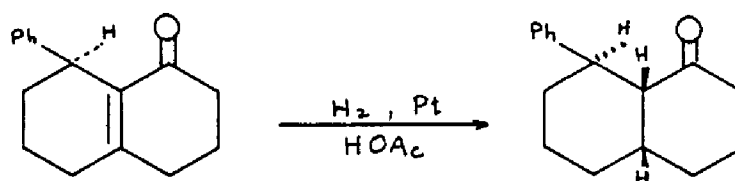


the γ -site leading to the vinylogous enolate [VII] and the α' -site giving the cross-conjugated enolate [VIII]. The α -site, for stereoelectronic reasons, will be of considerably lower acid strength in cyclic enones, since it cannot be involved in π -delocalization to the carbonyl group. It has been shown that the α' -site is slower by about an order of magnitude in endothermic deuterium exchange, compared to the γ -position¹⁴⁹. The difference in acidity¹⁴⁹ (determined by experiment) between the γ -sites ($\Delta H^\circ_{\text{acid}}$ of 360.3 \pm 2.5 kcal/mol) and α' -sites ($\Delta H^\circ_{\text{acid}}$ of 366.8 \pm 2.3 kcal/mol) in cyclohexenones is thus 6.5 \pm 0.4 kcal/mol. The MNDO (semiempirical molecular orbital calculation)¹⁴⁹ revealed that the acidity of α' -site in the cyclohexenones is 359.8 kcal/mol while that of the γ -site is 348.9 kcal/mol. Thus, the vinylogous site is favored by 6.5 \pm 0.4 kcal/mol in the cyclic enone¹⁴⁹ and MNDO calculations parallel this¹⁴⁹.

In 2,3-dialkylcyclohexanone synthesis, a reduction of C=C in 2,3-disubstituted cyclohexenones is carried out by

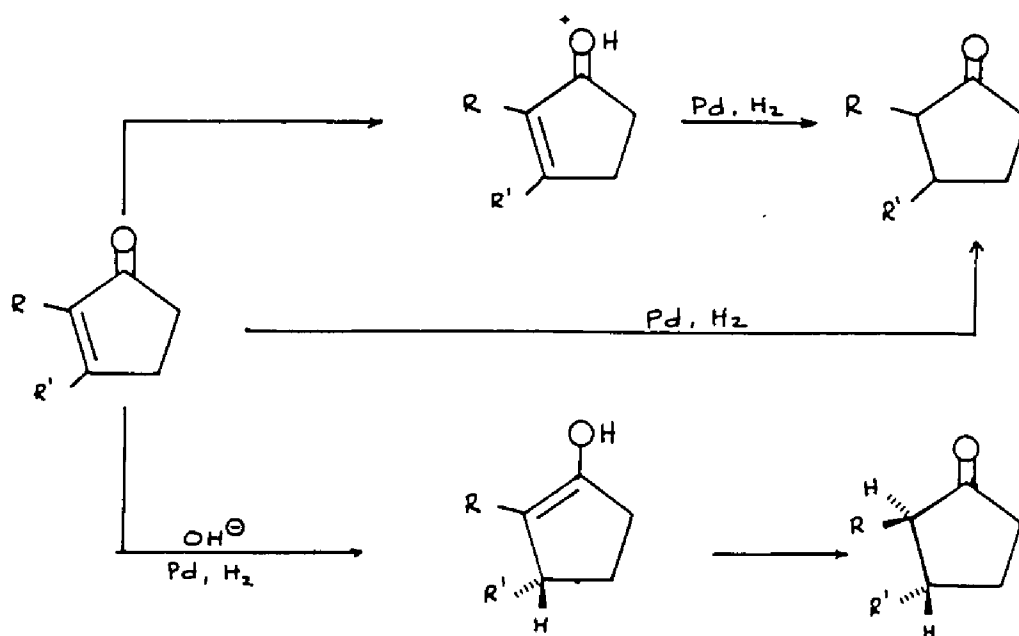
catalytic hydrogenation^{145a} or treatment with Li in NH₃¹⁵⁰. The stereochemistry of hydrogenation to the saturated ketone varies, depending on the reaction conditions: a cis product may be obtained under acidic conditions¹⁵¹, and a trans compound in the presence of bases¹⁵² (Scheme 53). The explanation of the phenomenon was given by Weid-

Scheme 53.



lich¹⁵² who considered that in the presence of acid, cis addition occurs directly to the -C=C- bond of the unsaturated oxo compound or its protonated form, while in

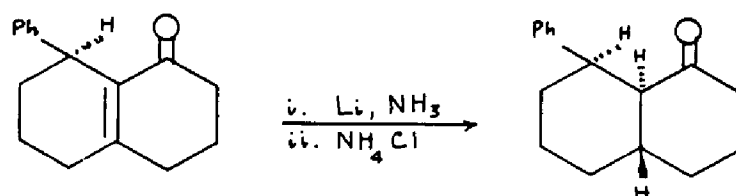
Scheme 54.



alkaline medium 1,4-addition occurs, followed by ketonization of the resulting enol to the trans compound (Scheme 54 above).

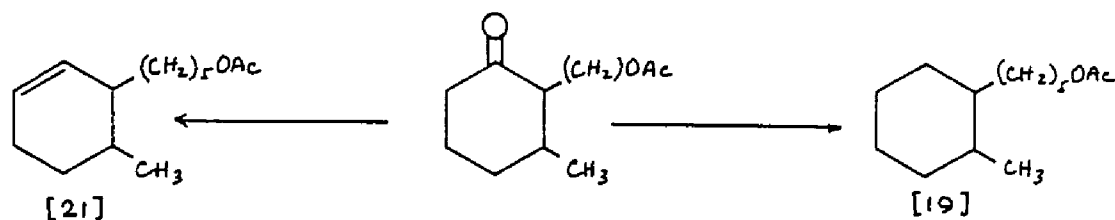
The metal reduction of α, β -unsaturated ketones usually yields a saturated ketone which has the more stable configuration at the β -carbon atom¹⁵². The configuration at the α -carbon atom, which is controlled by the nature of the protonation of the intermediate enolate, is usually of less concern, since the stereochemistry at this center is subject to change if the initial product is subjected to acid- or base-catalyzed enolization¹⁵³. The normal stereochemical outcome from Li/NH₃ reduction of 8-phenyl- $\Delta^{1,10}$ -octal-1-one is shown in the formation of the trans product¹⁵¹ (Scheme 55).

Scheme 55.



B. Syntheses of 6-membered ring pheromone analogs:

2-(5-Acetoxypentyl)-3-methylcyclohexanone [63], which could be prepared from either Hagemann's ester or 2-carbalkoxycyclohexanone, is a key intermediate in the synthesis of the pheromone analogs [21] and [19] (Scheme 56).



56). The preparation of the [63] will be discussed, followed by its conversions to [21] and [19].

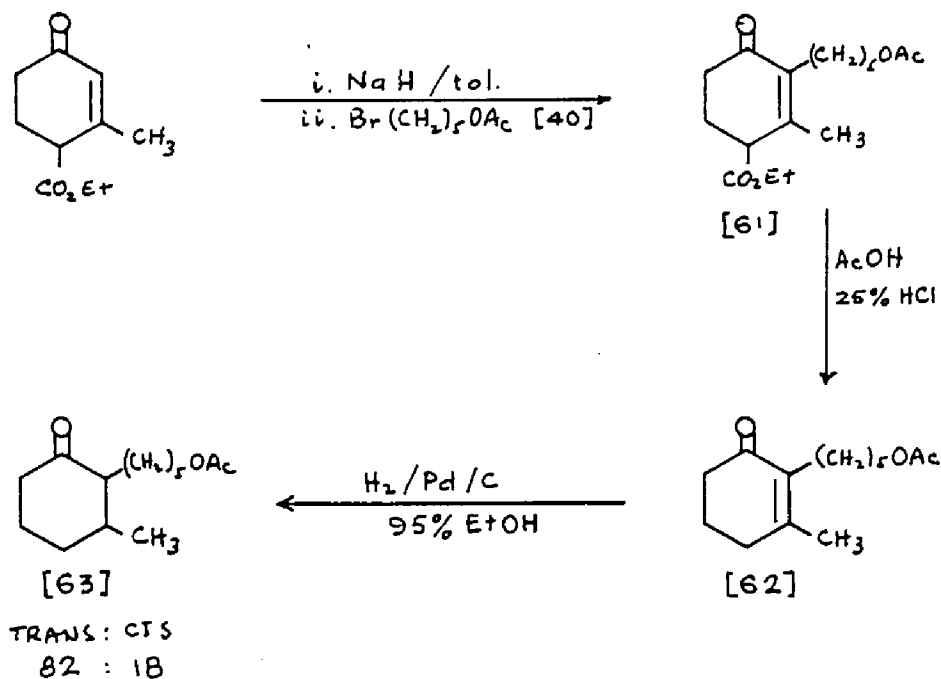
1. Preparation of 2-(5-acetoxypentyl)-3-methylcyclohexanone [63]:

a. Route from Hagemann's ester:

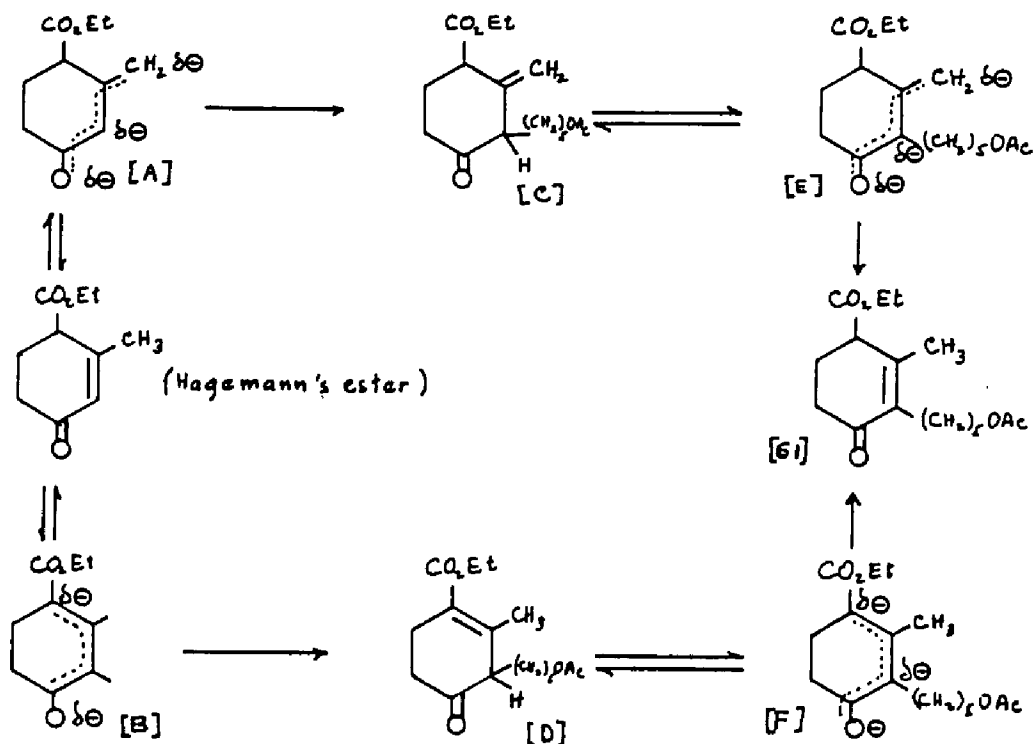
The synthesis of ketoester [63] commenced with ethyl 4-oxo-2-methyl-2-cyclohexenecarboxylate (Hagemann's ester). This material, upon alkylation with [40] afforded the 3-substituted derivative [61]. The carboxylic acid, prepared in situ by heating keto-ester [61] with 25% HCl in acetic acid, decarboxylated on prolonged heating to give cyclohexanone ester [62] in about 65% yield. Hydrogenation of [62] in 95% EtOH, catalyzed by 5% Pd/C, produced a mixture of cis- and trans-[63] in 18:82 ratio

in high yield (98%) (Scheme 57).

Scheme 57.



The alkylation of Hagemann's ester with 5-bromopentyl acetate may best be understood by consideration of the equilibria pictured in Scheme 58, which is similar to that proposed for alkylation^{1,23} of 3-methyl-2-cyclohexanone with bromides of structure $\text{Br}-(\text{CH}_2)_n-\text{Br}$. The base NaH

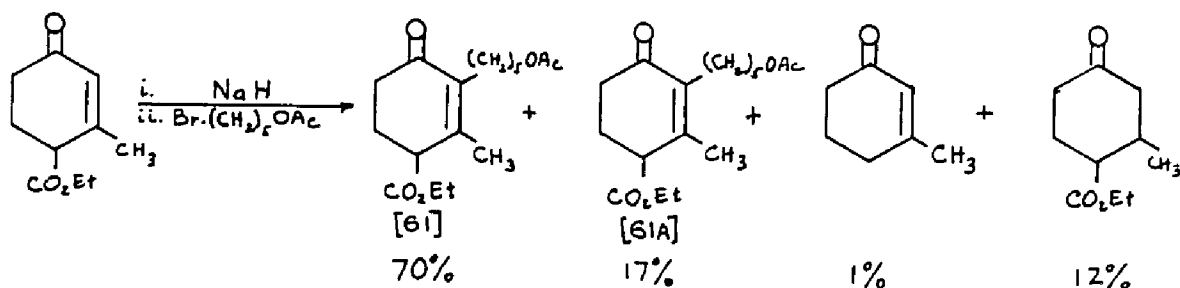
Scheme 58.

abstracts a proton from Hagemann's ester to give anions [A] and [B], each of which is alkylated preferentially at the carbon alpha to the carbonyl to give monoalkylation products [C] and [D], respectively. The base abstracts the alpha proton from [C] and [D] to yield anions [E] and [F], respectively, which preferentially form [G], having the $-\text{C}=\text{C}-$ double bond in conjugation with the ketone carbonyl.

There are some side products in the alkylation reaction of Hagemann's ester with 5-bromopentyl acetate such

as [61A] (17%), 3-methyl-2-cyclohexenone (1%), and a product of reduction at the $-C=C-$ double bond of Hagemann's ester (12%) besides the formation of [61] (70%) [based on GC] (Scheme 59).

Scheme 59.



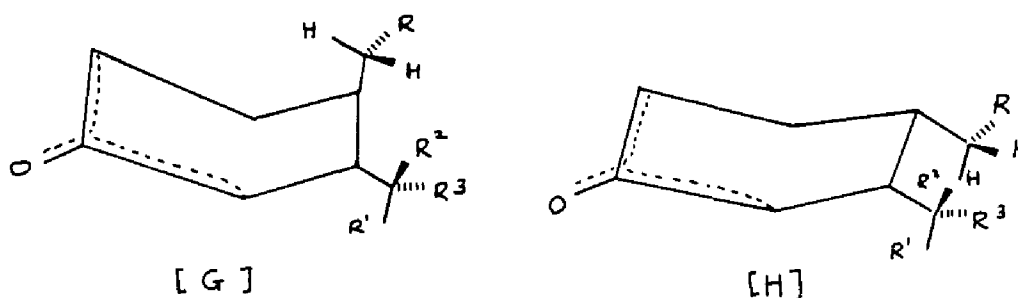
The ethoxycarbonyl group is removed (by hydrolysis and decarboxylation) when [61] is heated for some time with aqueous acid and co-solvent AcOH, forming [62]. The presence of AcOH is necessary to allow a smooth reaction to take place. The reaction is slow for the long chain alkyl derivatives, perhaps because of their poor solubility in aqueous acid without the co-solvent. Moreover, the cleavage of the acetate group in the alkyl chain of [61] could be avoided when a large amount of AcOH exists in the reaction mixture. In contrast, the use of ethanolic KOH for hydrolysis and decarboxylation of [61] is not a good way as it can convert ester in the alkyl chain to alcohol.

Palladium-catalyzed hydrogenation of [61] in 95% EtOH is a clean reaction without by-product formation and proceeds in 98% yield. Of the many reactions available for the reduction of organic compounds, catalytic hydrogenation offers the advantages of widespread applicability and experimental simplicity to a unique degree¹⁵⁴. That is a reason why hydrogenation is favored over reduction of the C=C with Li/NH₃. It is also possible to selectively reduce functional groups. For example, the reduction of an saturated ester or ketone to an unsaturated alcohol is normally accomplished with metal hydride reducing agents rather than by catalytic hydrogenation¹⁵⁵, whereas reduction of an unsaturated ester or ketone to a saturated ester or ketone is readily achieved by catalytic hydrogenation¹⁵⁶. The hydrogenation can be made selective by choice of catalyst, e.g. Pd catalyst fails to effect the reduction of ester to alcohol. The hydrogenation of [62] gives a higher yield when the reaction is run for 3 days at room temperature instead of 14 h. This reaction is slow, presumably due to the relatively crowded environment at the C=C of [62].

With respect to stereochemistry, it is interesting that [63], the hydrogenation product of [62], has a 82:18 trans:cis ratio (determined by ¹H NMR and GC). In hydrogenation of 1,2-dimethylcyclohexene, the Pd catalyst always gives the more stable

(trans) of the two possible products, while the cis-product is favored over a Pt catalyst¹⁵⁷. Stereochemistry in the Pd-catalyzed hydrogenation of 3,4-dialkylsubstituted cyclohexanones has been explained on steric ground^{157a}. The compounds containing a 3-Et group always gave more trans product than the 3-methyl compounds under the same reaction conditions, independent of the nature of the 4-alkyl. By analysis of the two adsorbed conformations of the enol form, it was pointed out that the cis-adsorbed conformation [G] is generally more favorable for the 3-Me compounds. If there is a C(3)-Et group, however, the catalyst hindrance means that this can be situated only in such a way that, as a result of the van der Waals interaction with the 4 substituent, the trans form [H] will be the more favorable adsorbed conformation^{157a} (Fig. 3). Steric

Fig. 3.



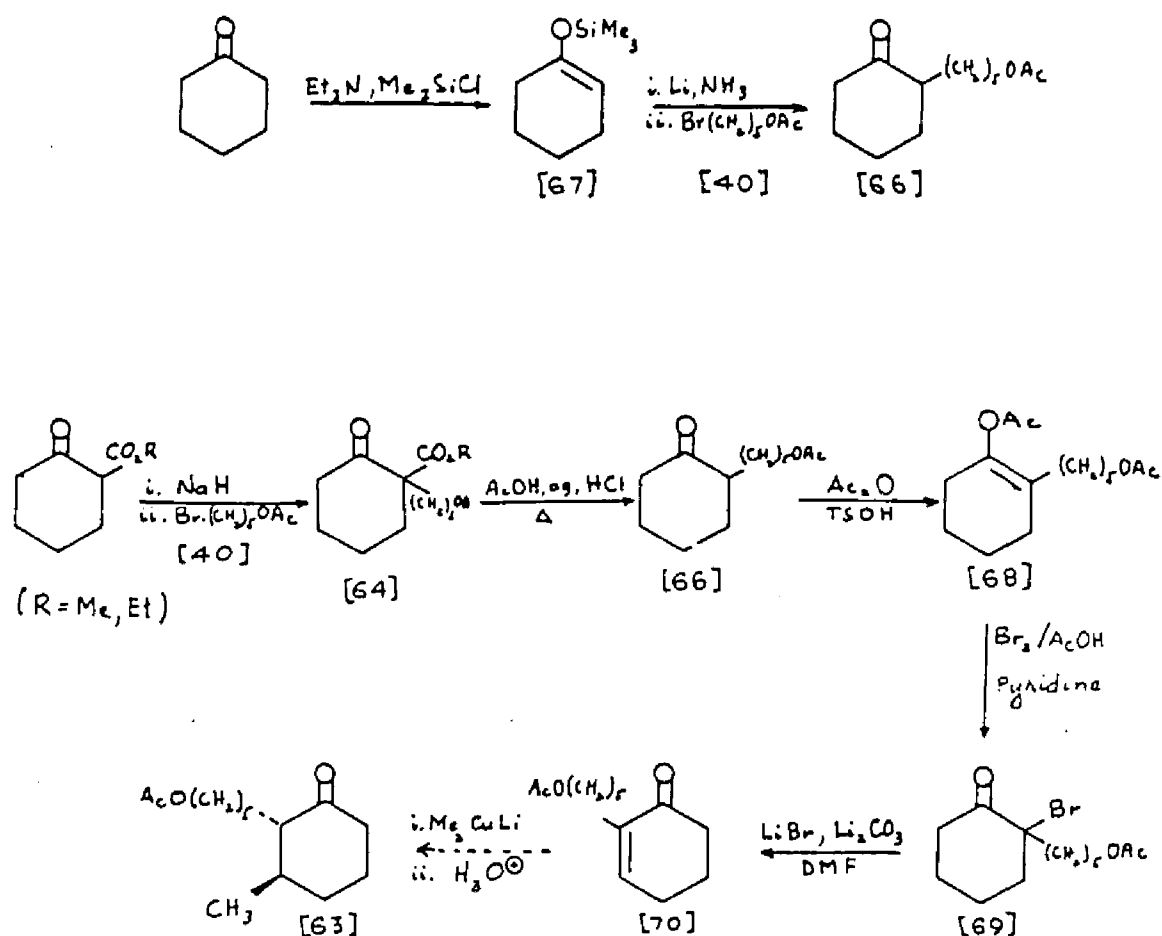
effects of a similar nature may be responsible for the results obtained in hydrogenation of [62]. An alternative explanation is that the 82:18 mixture simply repre-

sents the thermodynamic equilibrium mixture. Assignment of cis and trans stereochemistry of [63] will be discussed in a later section.

b. Route from 2-carbalkoxycyclohexanone:

The synthetic goal is the preparation of cyclohexenone [70] and its subsequent conversion to 2,3-dialkylcyclohexanone (Scheme 60). The sodium enolate of commercially available 2-carbalkoxycyclohexanone (60% ethyl,

Scheme 60.



40% methyl ester) was alkylated with bromoester [40] in DMF at 53°C to give crude product [64], which underwent hydrolysis and decarboxylation to ester [66] in ca. 83% overall (crude) yield (based on the mole ratio between ethyl and methyl of the starting material). The [66] was also obtained as follows: the silyl enol ether of cyclohexanone was converted to its Li enolate by treatment with Li in ammonia. Alkylation of this enolate with [40] gave [66] in 41% yield according to GC.

For the introduction of the required unsaturation, the general method of Bedoukian¹⁵⁹ which involves bromination of an enol acetate, was used to regiospecifically place bromine in the 2-position of the cyclohexanone ring. Other studies have shown that enolacetylation of 2-substituted cyclohexanones under equilibrating conditions results in predominant formation of the more substituted olefinic product¹⁶⁰. Thus, reaction of [66] with refluxing acetic anhydride in the presence of *p*-toluenesulfonic acid with removal of acetic acid by distillation gave a 98% yield of the desired enol acetate [68], which on treatment with bromine in acetic acid¹⁶⁰ afforded crude bromoketone [69]. The final step, dehydrobromination to the required cyclohexenone [70], was accomplished with LiBr-LiCO₃ in hot DMF¹⁶¹ (62% overall yield from [68]).

For the preparation of 11,15-dideoxyprostaglandins, the conjugate addition of organocuprates to cyclopente-

none has been a particularly useful procedure¹⁰³. The reaction of Me_2CuLi with cyclohexenone [70] by this method should give the desired conjugate addition product [63]. This procedure was not explored, since the desired [63] was obtained by the process already described starting from Hagemann's ester.

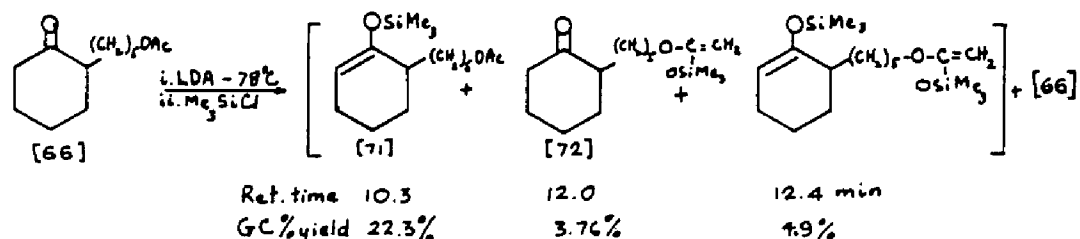
2. Conversion of [63] to 3-(5-acetoxypentyl)-4-methylcyclohexene [21] and 2-(5-acetoxypentyl)-methylcyclohexane [19]:

In a manner similar to the conversion of [37] to its corresponding cyclopentene [20] and cyclopentane [18], [63] was converted to [21] and [19] via hydroboration of its silyl enol ether and via reduction of its tosylhydrazone with sodium cyanoborohydride.

a. Conversion of [63] to [21]:

It is known that ketones and esters can form silyl enol ethers under the same standard conditions (LDA, -78°C , Me_3SiCl). Such was the case also for the keto ester [66] when treated with the base (1.2 equiv) and Me_3SiCl (1.8 equiv) at low temperature. A mixture of silyl enol ethers [71] and [72] was formed as shown in Scheme 61 below. To avoid the above problem, keto ester

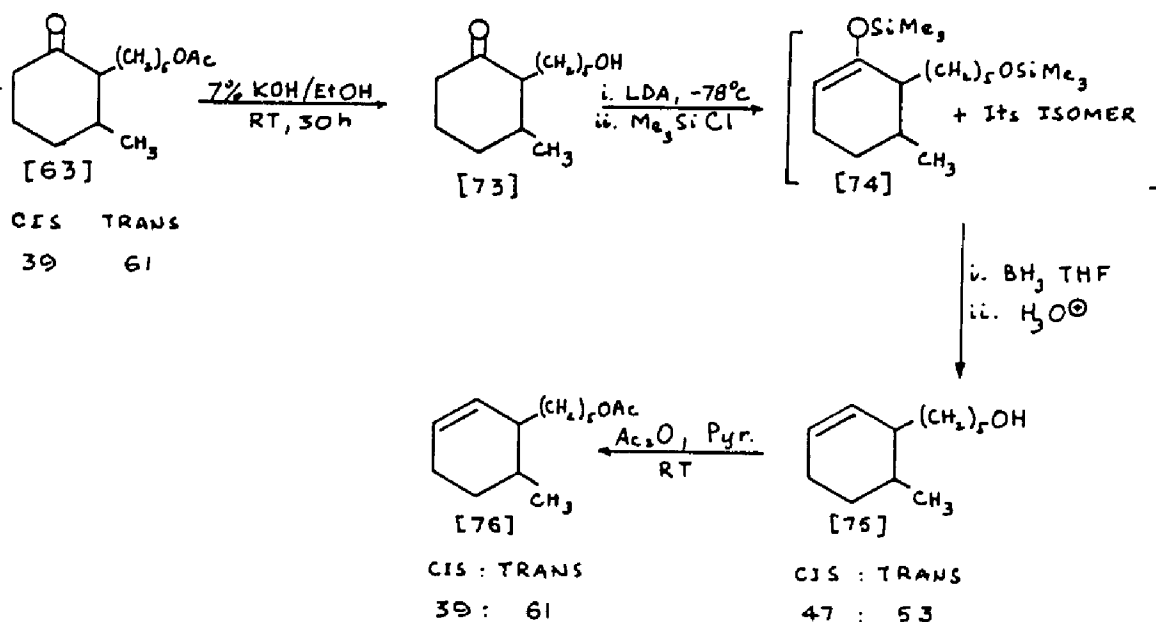
Scheme 61.



[63] with cis and trans ratio 39:61 was converted to keto alcohol [73] with cis:trans ratio 38:62 (according to 100 MHz ^1H NMR) before the formation of its silyl enol ether. The ester hydrolysis was accomplished by treatment with 7% ethanolic KOH at room temperature for 30 h. The reaction of [73] with LDA (2.26 equiv) and Me_3SiCl produced a mixture of silyl enol ether [74] (kinetic controlled) and its isomer (thermodynamic controlled) [ratio is 60:40 and retention time 13.4 and 13.6 min., respectively] which was hydroborated by $\text{BH}_3\cdot\text{THF}$. Work-up of the resulting reaction mixture in aqueous HCl provided cis- and trans-[75] in a 47:53 ratio (determined by 400 MHz ^1H NMR) in 63% yield. There was more cis-product in [75] than in the starting material [73], although the trans-product is still the major one. The alcohol [75] in pyridine was esterified by acetic anhydride to afford cis- and trans-[21] (39:61 ratio according to 400 MHz ^1H NMR)

in 80% yield, Scheme 62, (see stereochemical assignment section for the stereochemistry determination of [63] and [75]). The cis:trans ratios which change from 47:53 in [75] to 39:61 in [21] may be explained by a reaction of alcohol and $-C=C-$ bond. Marshall¹⁶² reported alcohols can be added to certain double-bond compound (cyclohexenes and cycloheptenes) photochemically. An observation of predominance of cis over trans isomers in photo-induced additions of alcohols to 1-menthene (cyclohexene derivative) can be understood on the basis of the 1-menthyl cation where steric factors favor approach from the bottom face. This fact could be used to explain the changes in the cis:trans ratios from 47:53 to 39:61.

Scheme 62.



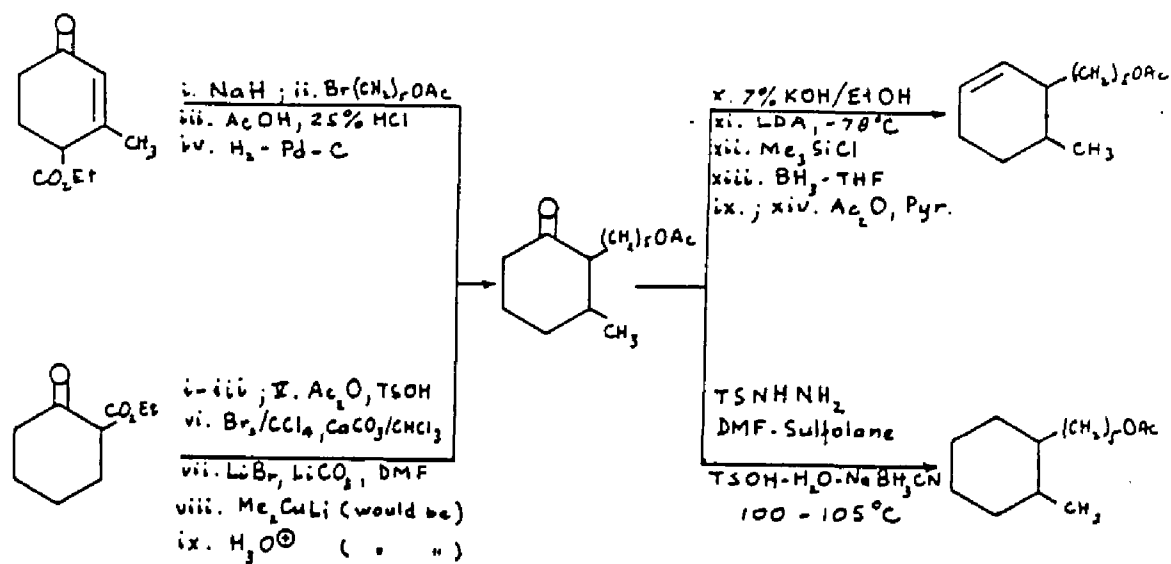
b. Conversion of [63] to [19]:

The keto ester [63] was converted to cyclohexane [19] by following the same procedure as described previously in the conversion of cyclopentanone derivatives to cyclopentanones. The cis- and trans- [19] in 18:82 ratio (determined by 400 MHz ^1H NMR) was reacted with p-toluenesulfonylhydrazine in DMF-sulfolane having p-toluenesulfonic acid monohydrate as a catalyst, and NaBH_3CN to give cis- and trans-[19] (ratio 39:61) in 17% yield, and starting material was recovered. The yield is low due to an incomplete conversion of [63] to its hydrazone. As previously stated, tosylhydrazone formation in DMF-sulfolane was extremely slow¹²⁷ and varying amounts of ketones were recovered unchanged even after several hours at 100 to 105°C. The trans/cis ratio decreased as the reaction proceeded (from 4.55 to 1.56) indicating that acid-catalyzed equilibration of the substituent adjacent to the tosylhydrazone group occurred, probably during its formation¹²⁷. The increment of cis-stereoisomer (from 18% to 39%) of the tosylhydrazone of [63] probably arises from the favored axial disposition of substituents adjacent to exocyclic $\text{C}=\text{N}^{162b}$. The stereochemical assignment of [19] will be discussed later.

The following Scheme 63 summarizes the total synthe-

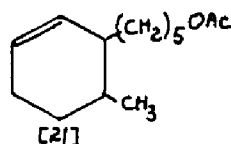
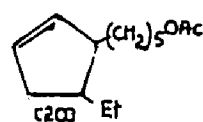
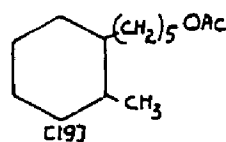
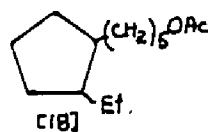
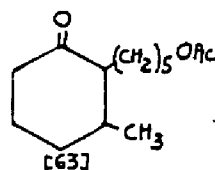
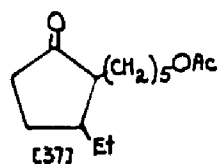
sis of the 6-membered ring pheromone analogs [21] and [19] from Hagemann's ester and 2-carbalkoxycyclohexanone.

Scheme 63.



IV. STEREOCHEMICAL ASSIGNMENTS OF [37],[63],[19-21]:

This section mainly deals with details of the stereochemical assignments of 2-(5-acetoxypentyl)-3-ethylcyclopentanone [37] and 2-(5-acetoxypentyl)-3-methylcyclohexanone [63]. Once their stereochemistries are fixed, the assignment of stereochemistry of the substituents on [18-21] may be done more easily. Although the conversion of [37] and [63] to [18],[20] and [19],[21], respectively, might alter the chiral centers in [37] and [63] via keto-enol tautomerism, the major isomers are the same as in the starting materials as discussed later in this section.



In general, the assignment of the stereochemistry at C-2/C-3 in cycloalkanones is established by (i) their ¹H- and ¹³C-NMR spectral data (ii) the method of synthesis (iii) the stereochemistry of analogs or (iv) their epimerization under alkaline conditions.

A. Stereochemical assignments for [37].

[37] was prepared by addition of lithium diethyl cuprate to 2-(5-acetoxypentyl)-2-cyclopentenone as discussed earlier. Conjugate additions of organocopper reagents with substituted cyclic enones are known to proceed with exceedingly high stereoselectivity to favor *trans* over *cis* adduct^{16a}. The synthesis depends on steric interactions to control the relative stereochemistry of the ring substituent. The protonation of the resulting enolate (derived from the conjugate addition reaction) selectively gives rise to the thermodynamically more stable stereoisomeric cyclopentanone. Thus, *trans*-[37] is expected to be the major isomer and *cis*-[37] the minor isomer based on the method of synthesis. The *trans*-configuration of [37] was further evidenced by its stability to basic conditions. Treatment with 7% KOH-EtOH at room temperature for 24 h or refluxing Et₃N produced no change in the ¹H NMR spectrum or TLC behavior.

The assignments for the stereochemistry of [37] were reinforced by ¹³C-NMR studies. [37] as prepared from the conjugate-addition of lithium diethylcuprate to 2-(5-acetoxypentyl)-2-cyclopentenone appears, from GC analysis to be mainly one isomer, which is being assigned the *trans* geometry. The 200 MHz ¹³C NMR spectrum of that product contains a set of strong signals corresponding to 12 aliphatic carbons (11.36, 20.88, 26.19, 26.43, 26.50, 27.25, 27.98, 28.39, 37.71, 43.24, 54.67 and 64.44 ppm) and 2 carbonyl carbon signals (171.23 and 217.16 ppm). Addition-

al minor signals (25.57, 28.10, 35.36, 40.62 and 53.28 ppm), the average intensities of which are <10% of those of the major signals, are also present and are being assigned to that cis isomer. (Fig. 4). The DEPT method ¹⁶⁴ in the 200 MHz NMR was used in the assignment of CH, CH₂ and CH₃ groups, especially DEPT 45°. CH₂ groups are separated from CH and CH₃ groups by DEPT 135°. Only CH groups are detected by DEPT 90°. The DEPT spectrum (Fig. 4) reveals carbon chemical shifts of (i) CH₃ groups at 11.36 and 20.88 ppm (one CH₃ of the Et group, the other of the acetoxy group) (ii) CH₂ groups at 25.57, 26.19, 26.43, 26.50, 27.25, 27.98, 28.10, 28.39, 35.36, 37.71, and 64.44 ppm (iii) CH groups at 40.62, 43.24, 53.28, and 54.67 ppm. Having assigned these resonances in the 200 MHz spectrum of the sample of [37] that consists of mainly one isomer, we can now look at the more complicated example in which both cis and trans isomers are present in comparable amounts. Figure 6 shows the proton-decoupled ¹³C spectrum (and corresponding DEPT spectra) of [37] prepared by conjugate addition - alkylation. This 200 MHz spectrum contains resonances from a 3rd isomer, but these resonances do not appear to be complicate any of the assignments to be discussed below. Among the CH₂ groups, assignment of the methylene carbon attached to C-2 of the cyclopentanone ring (*) and the methylene carbon attached to C-3 of the ring (**) (see Table 2) were based on analogy with ¹³C chemical shifts reported in literature data for prosta-

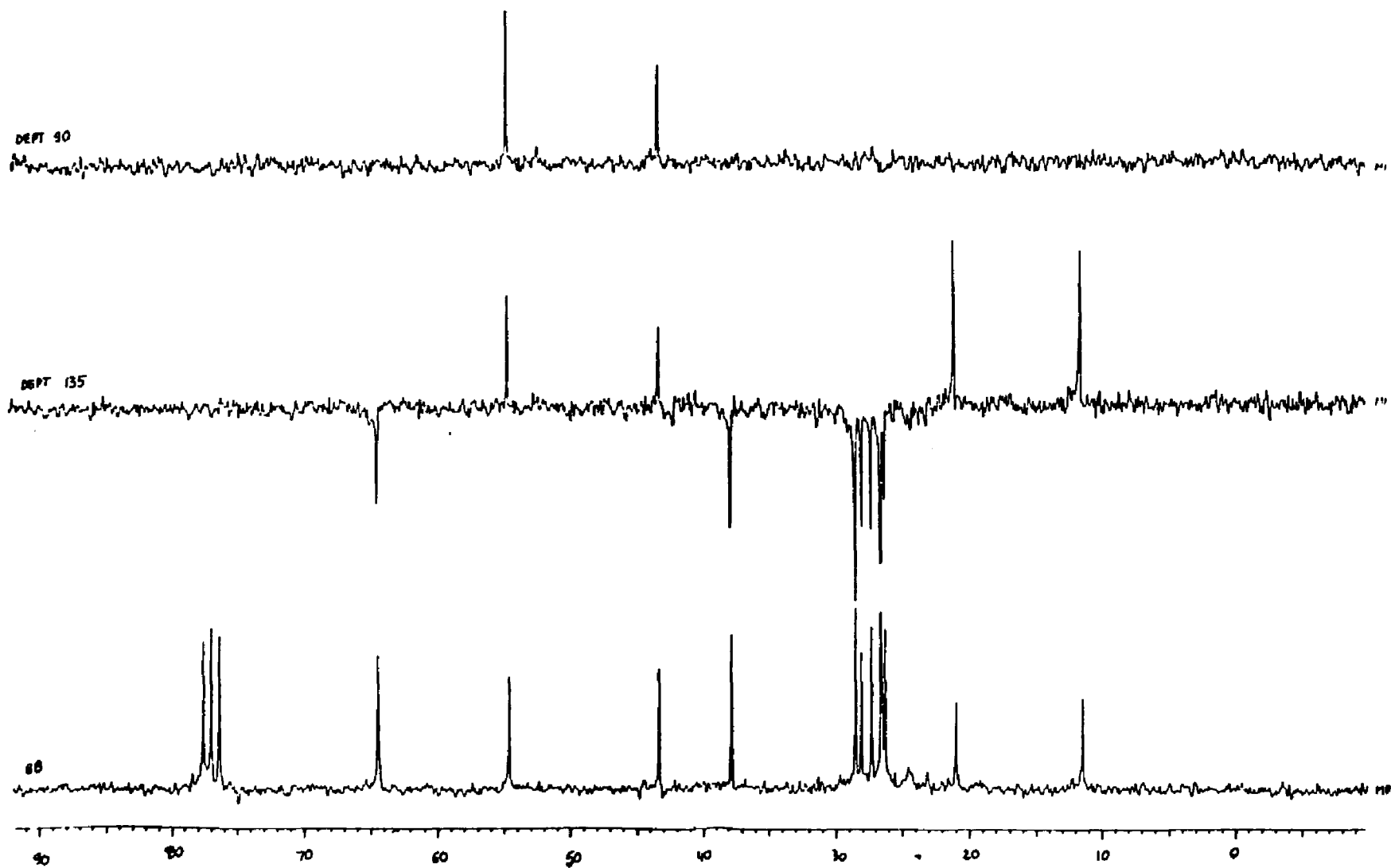


Fig. 4 and 5 : 200 MHz ^{13}C -NMR-DEPT SPECTRUM OF [37] (PREPARED FROM 2-ALKYL-2-CYCLOPENTENONE)

glandins ^{165,166}, cyclopentanone derivatives¹⁶⁷ and the spectroscopic data for 2-(5-acetoxypentyl)cyclopentanone [43] and 3-ethylcyclopentanone [36] (see Experimental Section) in which carbon chemical shifts in cis isomers appear upfield from those in trans isomers. The literature data ¹⁶⁸ suggested the chemical shifts of the ^{*}CH₂ to be 27.98 and 25.57 ppm in the 200 MHz ¹³C-NMR (Fig. 6) of [37] (prepared from 2-cyclopentenone route via conjugate addition - alkylation) for trans and cis stereochemistries, respectively. The carbon chemical shift assignment for the ^{**}CH₂ requires the assistance from ¹H NMR of 3-ethylcyclopentanone [36] which showed the chemical shift of the methylene proton in the Et group to be at 1.3 ppm. That chemical shift is the same in [37] as in [36] confirmed by the 2D-COSY¹⁶⁴ NMR of [37] (Fig. 7) which gives the connectivities of the coupled nuclei (¹H in this case). The COSY-90 spectrum of [37] (Fig. 7) shows that there are 2 groups of protons (CH₃ and CH at C-3 of the cyclopentanone ring) coupling with the CH₂ protons of the Et group, thus confirming the assignment of the methylene protons. A 2D-¹³C-¹H chemical shift correlation spectrum¹⁶⁴ of [37] is now obtained to assign the carbon chemical shift of the ^{**}CH₂ group. From this map (Fig. 8), multiplets in the 200 MHz ¹H NMR could be correlated with ¹³C signals. Thus the carbon chemical shifts of ^{**}CH₂ are assigned as 28.4 and 28.1 ppm for trans- and cis-[37], respectively, which are in agreement with literature data on cyclopentanone

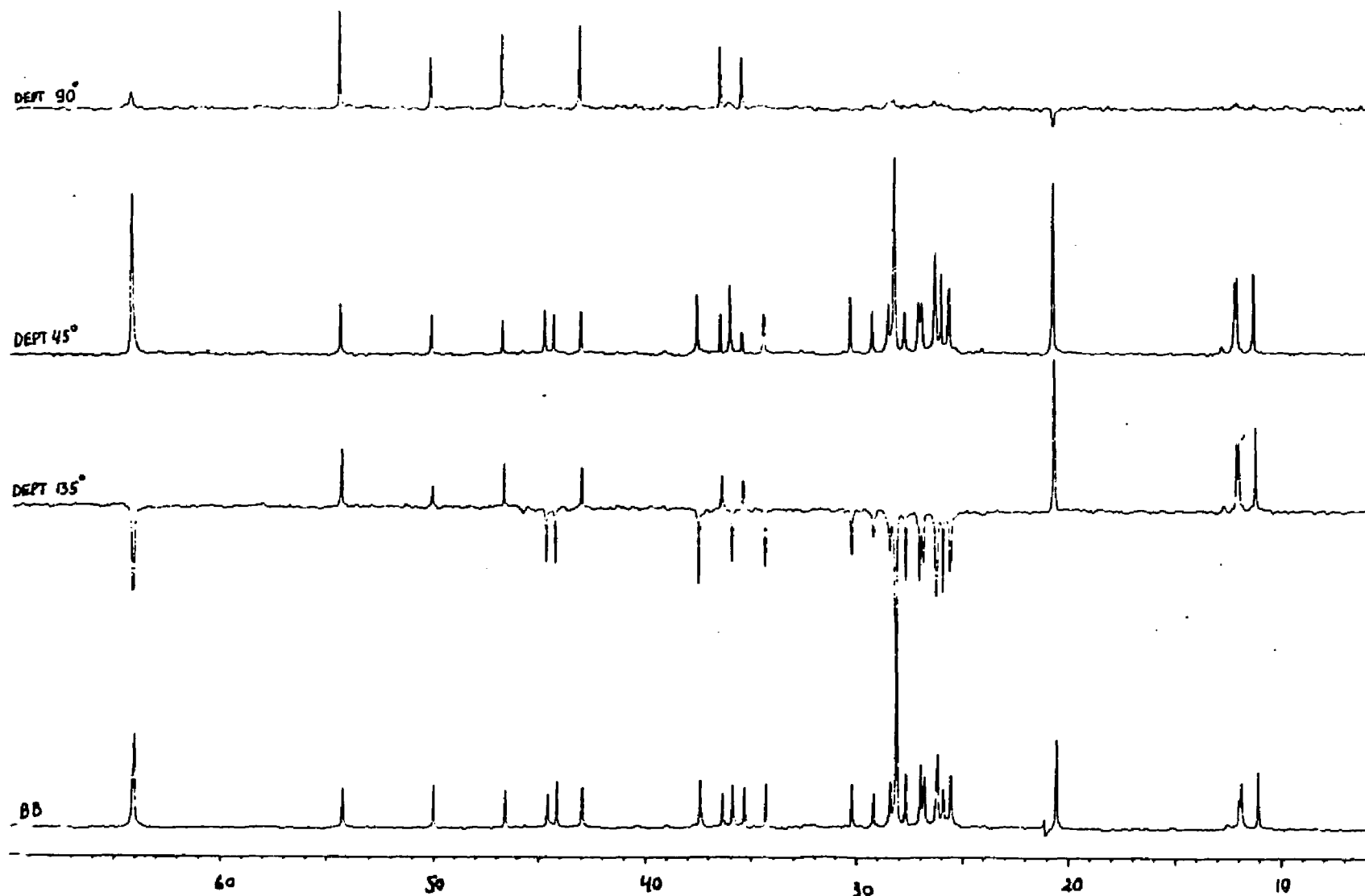
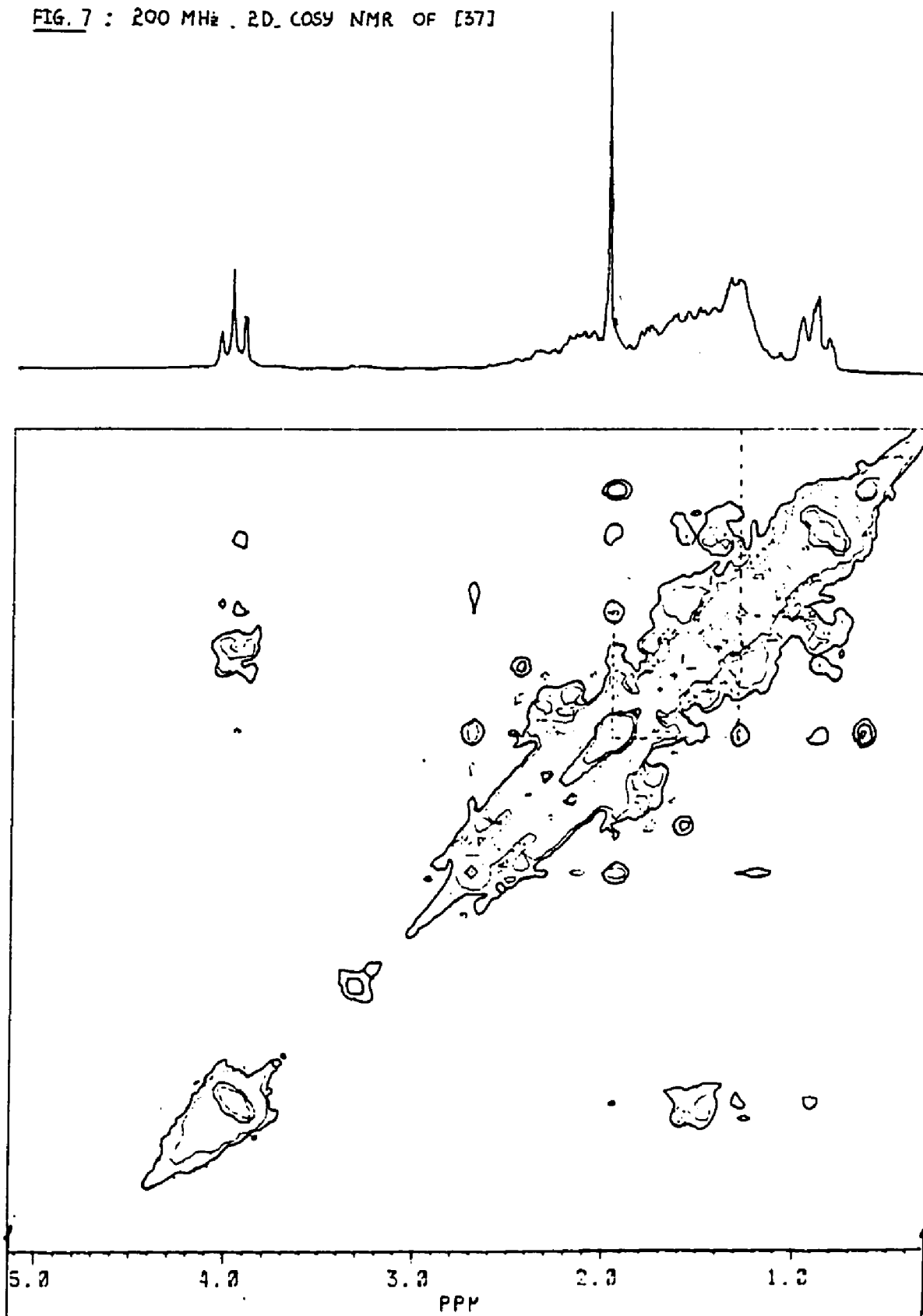


Fig. 6 : 200 MHz ^{13}C NMR OF [37] COMBINED WITH DEPT METHOD.

FIG. 7 : 200 MHz . 2D. COSY NMR OF [37]



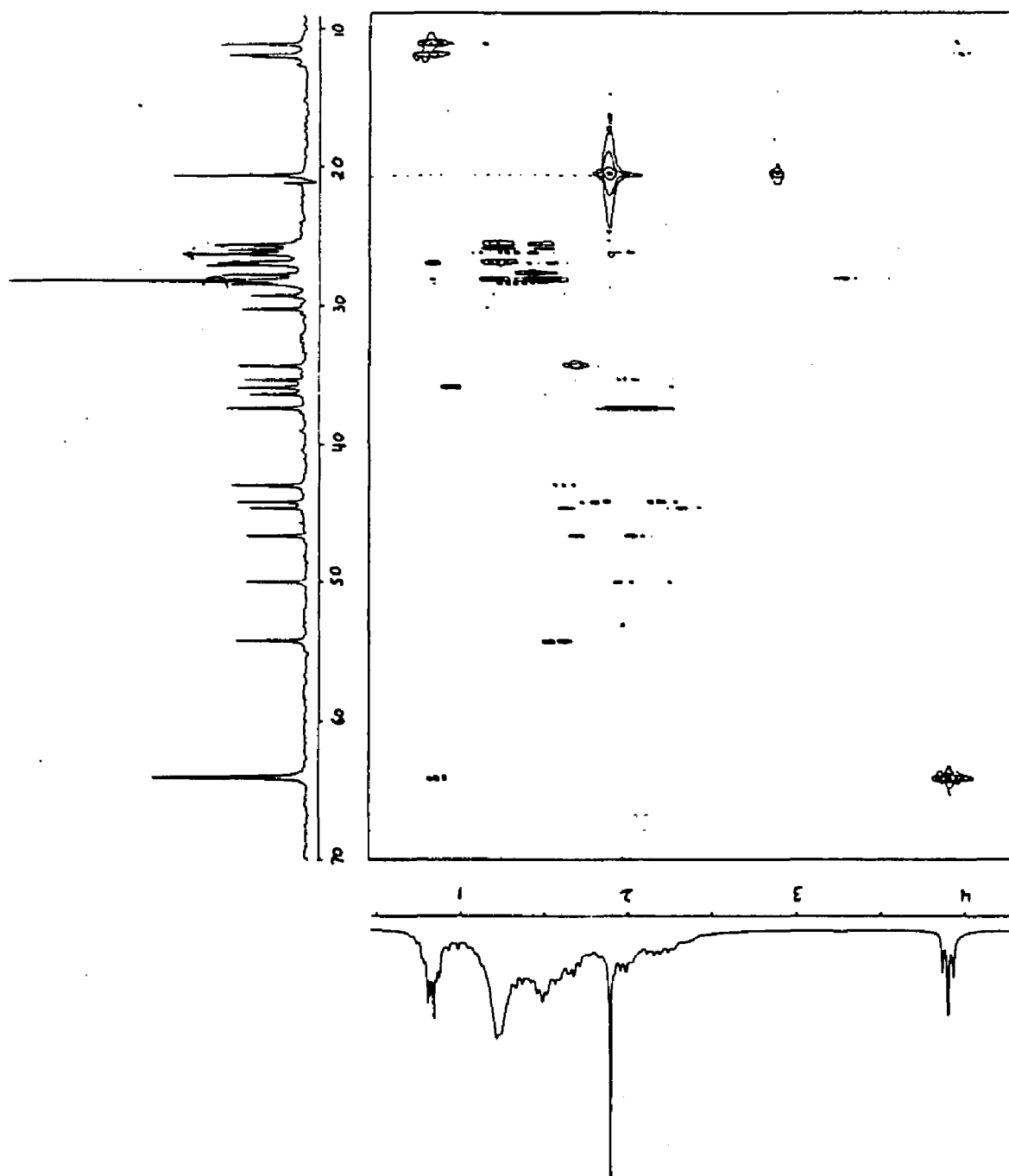
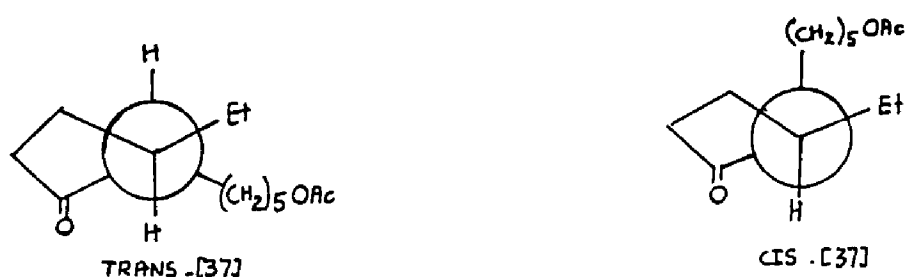


FIG. 8: 2D ^{13}C - ^1H CHEMICAL SHIFT CORRELATION SPECTRUM OF [37] IN CDCl_3 200 MHz.

derivatives¹⁶⁷. These chemical shifts of $^*\text{CH}_2$ and $^{**}\text{CH}_2$ are used in the stereochemical assignment of [37] as seen in the following paragraph.

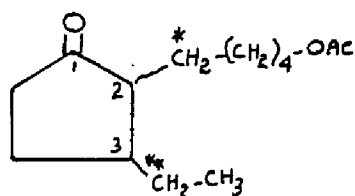
The methylene carbon (attached to C-2 of the cyclopentanone ring) and the methylene carbon (attached to C-3 of the ring) are γ to one another, and their chemical shifts vary depending upon the relative positions of those carbons to each other in space. A carbon three bonds distant from a substituent has been shown to exhibit an upfield shift due to sterically induced polarization of the C-H bonds¹⁶⁸. In rigid cyclic systems this effect is at a maximum when the substituent and the γ carbon are gauche (γ -gauche effect). Thus in [37] the effect should be greater in the cis-isomer where the carbons are gauche than in the trans-isomer, where the carbons are anticlinal (Fig. 9). Table 2 gives the observed shifts as discussed

Fig. 9.



above and allows assignment of stereochemistry in [37] since both methylene groups marked with asterisks are upfield in the isomer assigned the cis stereochemistry. This technique (γ -gauche effect) has also been applied to analogous systems.¹⁶⁶

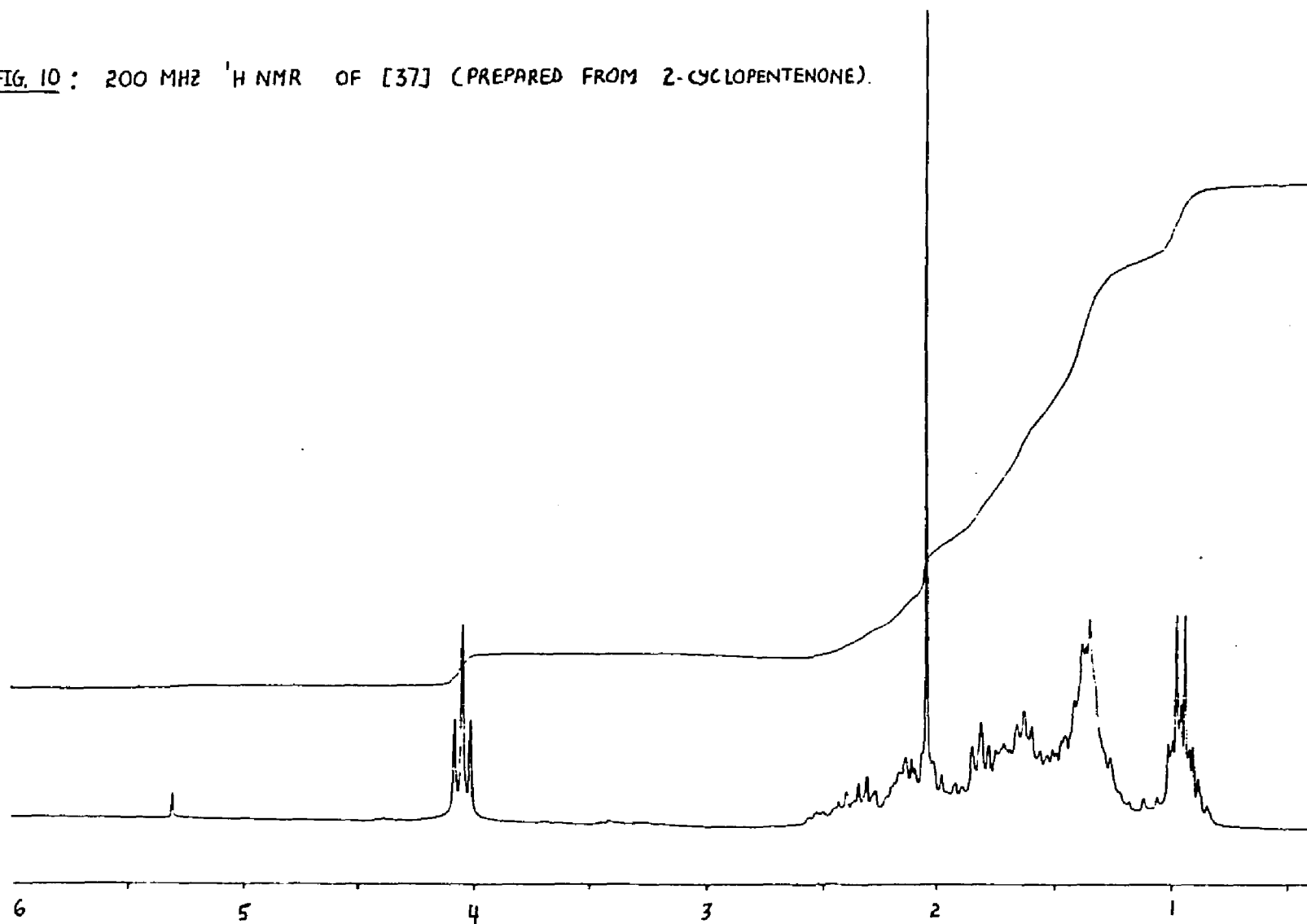
Table 2



<u>^{13}C shifts (ppm)</u>		<u>Stereochemistry.</u>
$^*\text{CH}_2$	$^{**}\text{CH}_2$	
27.98	28.39	Trans.
25.57	28.10	Cis.

As previously mentioned, the 400 MHz ^{13}C -DEPT spectra of the mixture isomers of [37] showed 4 distinct α - and β -methine carbon resonances at δ 53.3, 40.6 in cis and δ 43.2, 54.7 in trans isomer (Fig. 5). This assignment is supported by Tan's report^{167c} on cis- and trans-2,3-dimethylcyclopentanone. The trans stereochemistry in [37] was also identified by utilizing ^1H , ^{13}C -NMR and DEPT in the high field NMR, combined with 2D ^{13}C - ^1H correlation spectra to determine the C_2H - C_3H coupling constant as explained next. The already-assigned chemical shifts of the methine carbon at δ 50.0 ppm for cis-[37] and 46.6 ppm for trans-[37] were correlated to proton chemical shifts on the 2D ^{13}C - ^1H correlation spectrum (Fig. 8) which were then referred to the 200 MHz ^1H -NMR (Fig. 10) and assigned to be at δ 2.0949, 2.0636 ppm and δ 2.1623,

FIG. 10 : 200 MHz ^1H NMR OF [37] (PREPARED FROM 2-CYCLOPENTENONE).

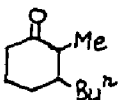
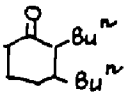
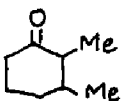
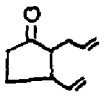
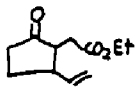


2.1073 ppm, respectively. The figures 0.0316 and 0.0550 ppm from the subtraction of two pairs 2.0949, 2.0636 and 2.1623, 2.1073 were multiplied by 200 (since the 200 MHz NMR spectrum was used) to give the C_2H-C_2H coupling constants, 6.3 Hz for cis [37] and 11 Hz for trans [37]. The value 11 Hz is in the region characteristic of trans-2,3-dialkylcyclopentanones but too large for a cis-2,3-dialkylcyclopentanones ^{169a}, whose coupling constant between 2 methine protons is 6.3 Hz.

Gas chromatography (SE-30 column) is also helpful in the stereochemical determination. Cis-2,3-dialkylcycloalkanones (5- and 6- membered rings) have longer retention times than do their trans counterparts ⁹⁴. Table 3 shows five known examples to support the statement above. The retention time of the minor component in the mixture of [37] isomers, which was assigned the cis stereochemistry by NMR, was 11.8 min., and that of trans [37] was 11.5 min.

Table 3.

Retention times of cis- and trans-
2,3-dialkylcycloalkanones.

<u>Entry</u>	<u>Compound</u>	<u>Stereochemistry</u>	<u>Glpc column</u>	<u>Ret. time</u>	<u>Ref.</u>
1		CIS	C	10.8 min	54
		TRANS	C	10.5	"
2		CIS	C	10.3	"
		TRANS	C	9.5	"
3		CIS	D	longer than	169b
		TRANS	D	shorter "	CIS
4		CIS	A	7.0	54
		TRANS	A	6.5	"
5		CIS	C	9.0	"
		TRANS	C	7.8	"

Note: Glpc column:

- A. 10 ft x 0.25 in. FFAP on Chrom W (60-80).
- C. 9 ft x 1/8 in. 5% SE-30 on Chrom G (100-140).
- D. 10 ft x 0.25 in. 20% Dow 550 silicone on Chromosorb W.

B. Stereochemical assignments for [63].

The assignment for cis- and trans-[63] were based on the fact that protons on a five- or six-membered ring α to a substituent (such as alkyl groups) are more shielded when they are cis to this substituent than when they are trans¹⁷⁰ and based on the generalization observed by Pfeffer and Osman¹⁷¹ that C(3)-methyl substituents

in the cis isomers of 2,3-dialkylcycloalkanones appear upfield ($\Delta\delta$ 0.22-0.28) relative to that of the corresponding methyl in the trans isomer.

Based on the generalization above, assignment for cis and trans stereochemistries for [63] was based on ^1H NMR. The Me group of cis-[63] (minor isomer) and trans-[63] (major isomer) occurred at 0.81 and 1.13 ppm, respectively, and appeared as doublets with coupling constants 7.0 Hz and 6.6 Hz, respectively, due to the fact the Me of the cis isomer is shielded as seen in Pfeffer and Osman's generalized observation.

The mixture was analyzed by GC on a 30m-SE-30 column, the retention times for the major and minor isomers were 13.5 and 13.6 min respectively. Thus, since the major isomer has been assigned the trans geometry based on NMR, it is the isomer with shorter retention time. This is in agreement with previous observations. These ^1H NMR and GC data are in agreement with those for cis- and trans-2-allyl-3-methyl-cyclohexanone¹⁹².

The stereochemical assignments for [63] were also based on ^{13}C -NMR observations and coupling constants of the two methine protons. The arrangement of the 2 side-chains at C_2 and C_3 of [63] was deduced from the magnitude of $J_{\text{C}-2\text{H},\text{C}-3\text{H}}$ (about 5.9 Hz for the cis-[63] and 11.0 Hz for the trans-[63])¹⁷². The ^{13}C NMR spectrum of [63] contained one set of 12 aliphatic signals (20.52, 20.99, 26.13, 26.97, 26.71, 27.03, 28.46, 33.14, 38.31, 41.50,

55.29, and 64.56 ppm) and 2 carbonyl carbon signals (171.22 and 213.17 ppm). Additional minor signals (14.5, 23.64, 25.49, 26.05, 26.28, 31.46, 36.33, 41.27, 55.03, 64.48 are also present (Fig. 11). The spectral data indicated that [63] was a mixture of trans and cis isomers. In a manner similar to the assignments of CH, CH₂, CH₃ group in [37] as discussed earlier, the ¹³C-DEPT-NMR spectrum (Fig. 12) of [63] gave carbon chemical shifts of (i) CH₃ attached to the ring at 14.50 (minor) and 20.52 ppm (major), and CH₃ attached to an acetoxy group at 20.99 ppm (ii) CH₂ groups at 26.13, 26.97, 26.71, 27.03, 28.46, 33.14, 41.50, 64.56 ppm (major) and 23.64, 26.05, 26.28, 31.46, 64.48 ppm (minor peaks) (iii) CH groups at 38.31, 57.28 (major) and 36.33, 55.03 (minor). (These assignments were confirmed by ¹³C-¹H shift correlation spectrum (Fig. 13).) Among carbon chemical shifts of the CH₃ group, 20.5 ppm was assigned to trans and 14.5 ppm to cis-[63] based on the fact that methyl groups in a cis configuration shield each other more effectively than when they are trans^{17a}. The chemical shifts of the methylene carbon attached to C-2 of the cyclohexanone ring (*CH₂) were assigned to peaks at 28.4 ppm for the trans isomer and at 25.49 ppm for the cis isomer by analogy with literature data for cyclohexane^{17a} and cyclohexanone derivatives^{17b}.

γ-gauche effect has been discussed previously. In the cis isomer of [63] the effect causes an upfield shift of the signals for both *C and **C relative to those

FIG. 11 : 400 MHz ^{13}C -NMR SPECTRUM OF [63].

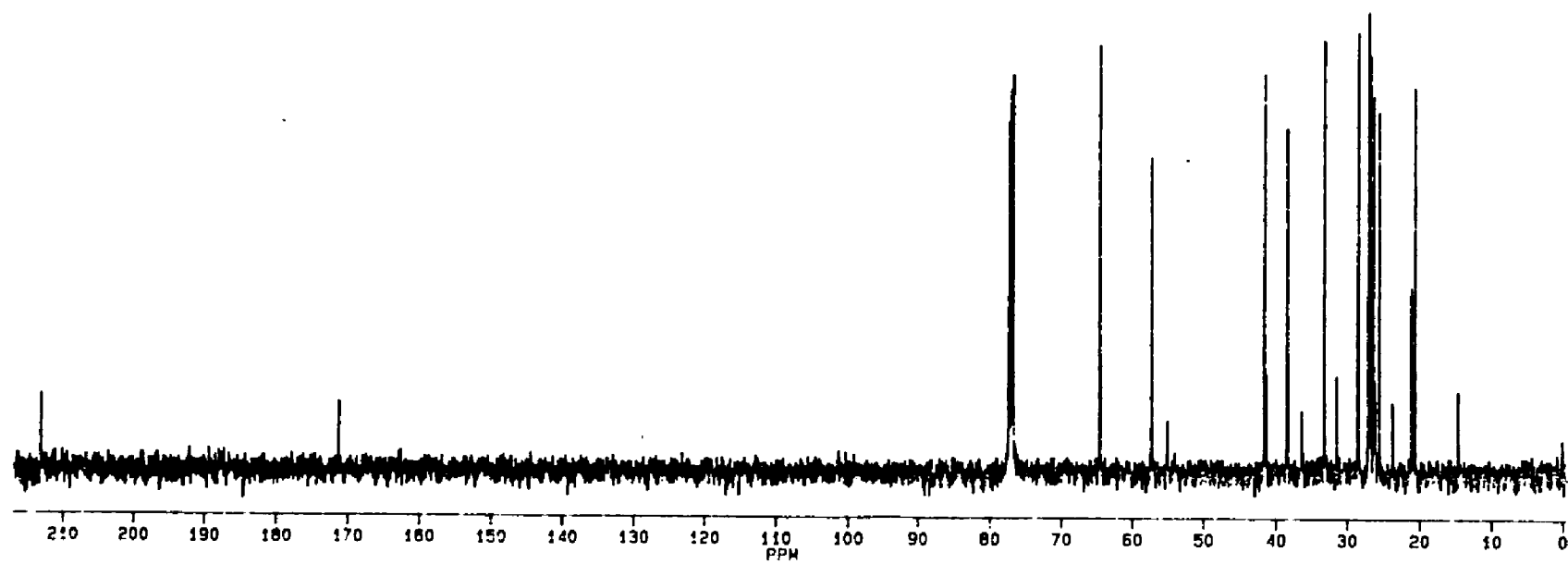
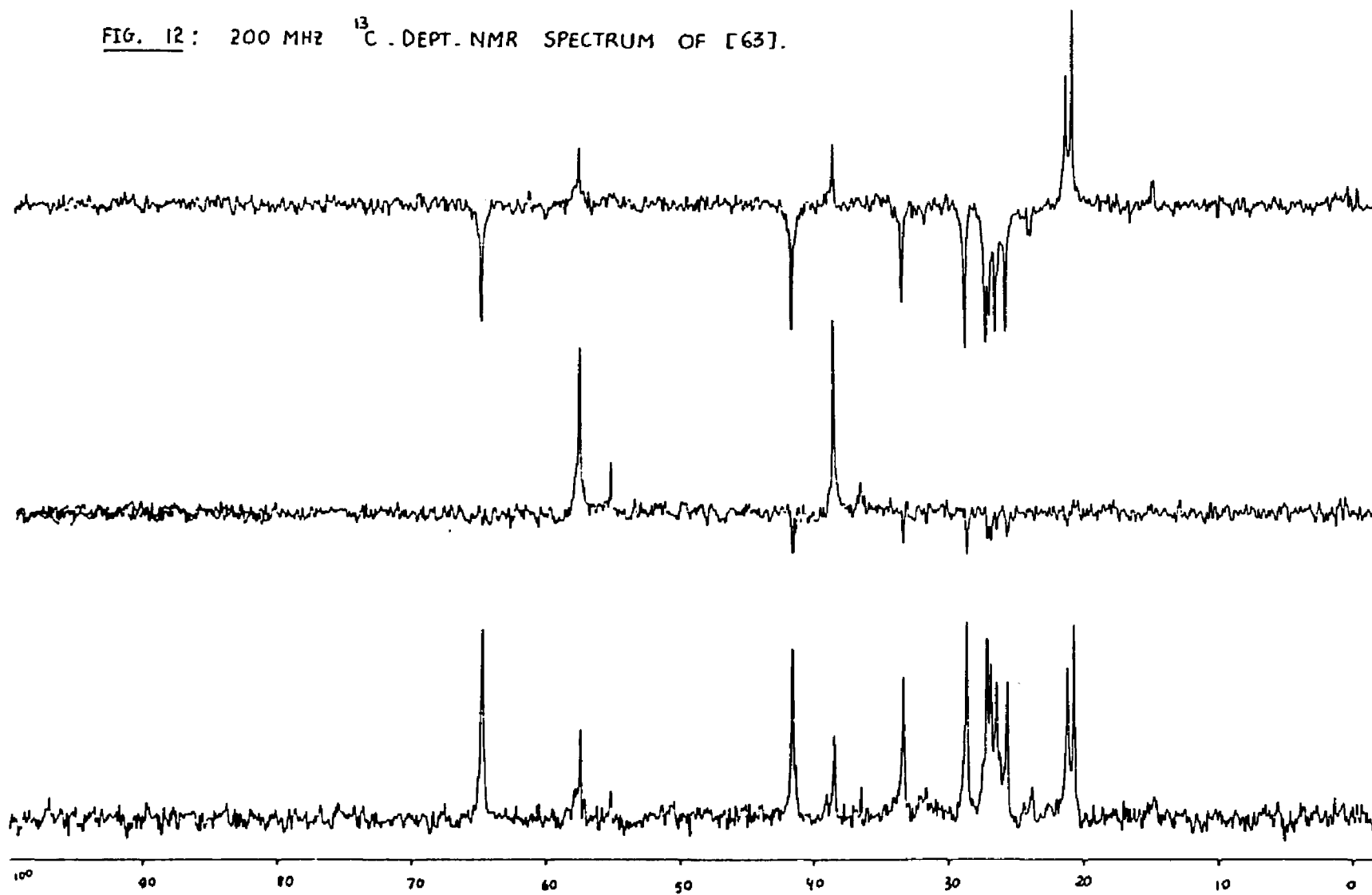


FIG. 12: 200 MHz ^{13}C DEPT-NMR SPECTRUM OF [63].



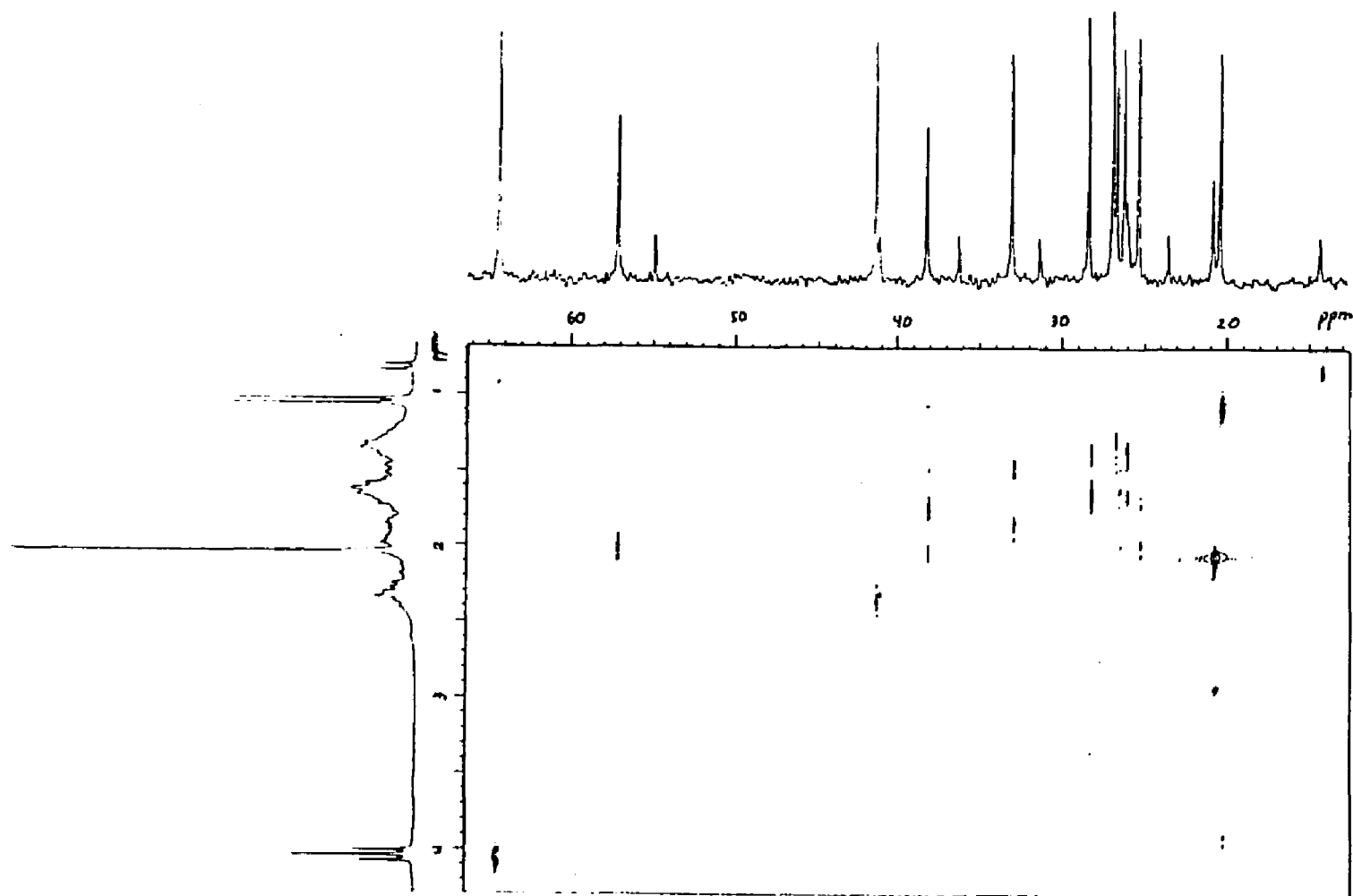
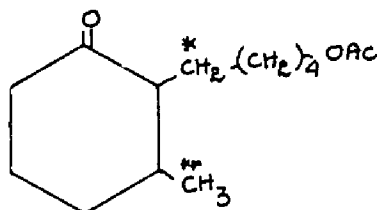


FIG. 13 : 200 MHz ^{13}C - ^1H SHIFT CORRELATION SPECTRUM OF [63].

in the trans isomer of [63] as shown in Table 4 .

Table 4



<u>^{13}C shifts (ppm)</u>		<u>Stereochemistry.</u>
$^*\text{CH}_2$	$^{**}\text{CH}_2$	
28.40	20.5	Trans.
25.49	14.5	Cis.

A comparison of the ^{13}C chemical shift values for the cis- and trans-[63] showed that ring carbons at α - and β -position are at higher field in Cis (54.9 and 36.2 ppm, respectively) than in trans (57.2 and 38.2 ppm, respectively). These assignments are based on comparison with ^{13}C NMR spectra of 2- and 3-methylcyclohexanone¹⁷⁶ and 1,2-dimethylcyclohexane¹⁷⁴.

The assignment of trans stereochemistry is consistent with the observation that the isomer was not epimerized by exposure to ethanolic potassium hydroxide, whereas the cis isomer does undergo epimerization.

C. Stereochemical assignments of [20] and [21].

The stereochemistry of [20] was assigned according to analysis of ^1H , ^{13}C -DEPT, ^1H - ^{13}C shift correlation NMR (400 MHz). The trans- and cis-relationship of the 2 alkyl groups could not be determined by NMR spectroscopy directly on a mixture of [21] because insufficient product was available to obtain ^{13}C NMR and ^{13}C - ^1H shift correlation spectra of [21]. However, such spectra were obtained for the precursor, the alcohol [75]. Acetylation of trans- and cis-[75] produced trans- and cis-[21] having the same isomer ratios. Neither heat nor acid nor base catalyst was applied during the acetylation reaction to cause any loss of stereochemical integrity.

[75] and [20] were stereochemically homogenous with their starting materials [63] and [37], respectively, as deduced from ^1H NMR, in spite of the newly formed double bonds in [75] and [20]. Jaenicke and Boland¹⁷⁷ reported a good, handy method to determine stereochemical assignments of a series of 6 multifidens derivatives which are 3,4-disubstituted cyclopentenones (Table 5). The tertiary protons of the cis-multifiden were located at δ 2.9 (C4) and 3.6 (C3), whereas the corresponding trans-isomer showed resonances at δ 2.6 and 3.3 respectively. This correlation can be applied in the present work after the assignments of the C3 and C4 peaks in the ^{13}C and ^1H -NMR spectra of [75] and [20] are made. The ^{13}C -DEPT-NMR spectrum (Fig. 14) of the mixture of [20] isomers contained major CH signals at δ 45.72 and 51.56 ppm (the minor sig-

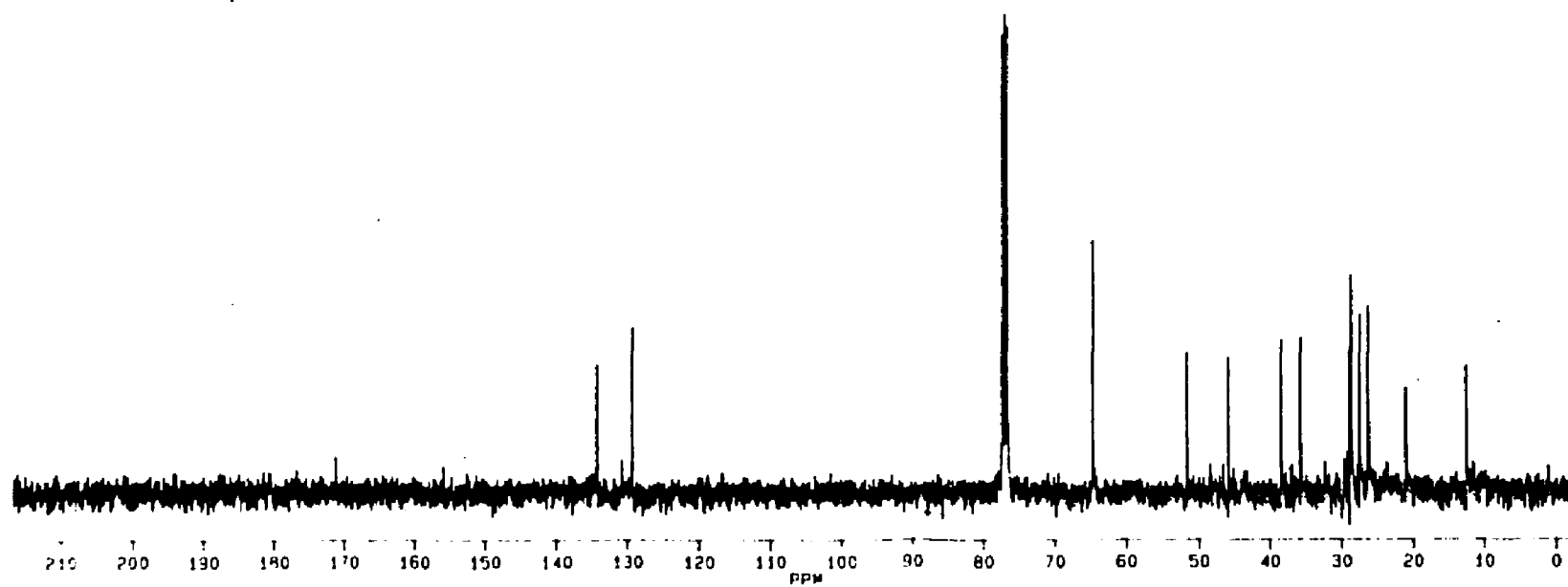
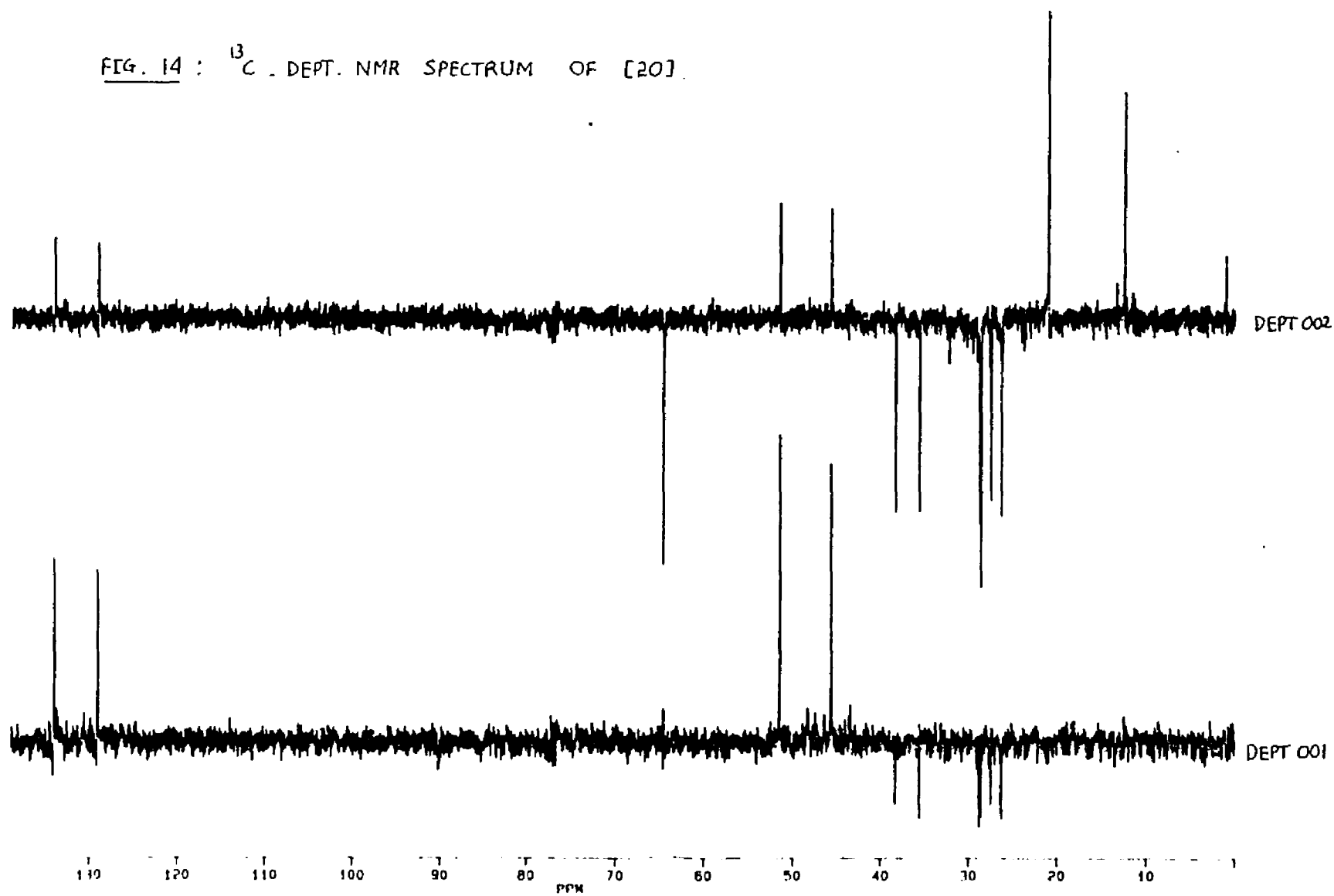


FIG. 14: ^{13}C -NMR SPECTRUM OF [20] (DEPT SPECTRUM IS IN ANOTHER PAGE).

FIG. 14 : ^{13}C - DEPT. NMR SPECTRUM OF [20]



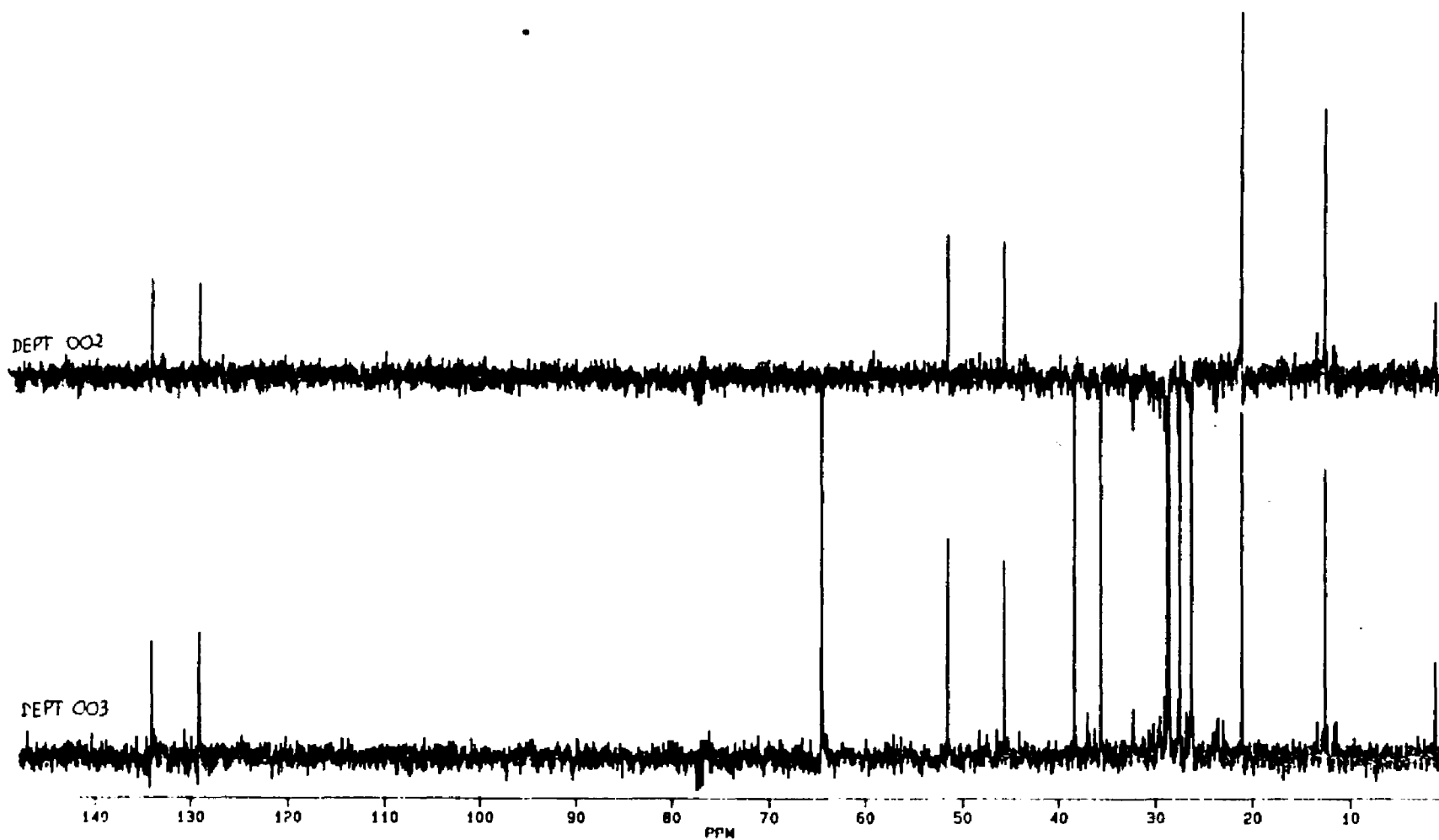


FIG. 14: ^{13}C DEPT. NMR SPECTRUM OF [20].

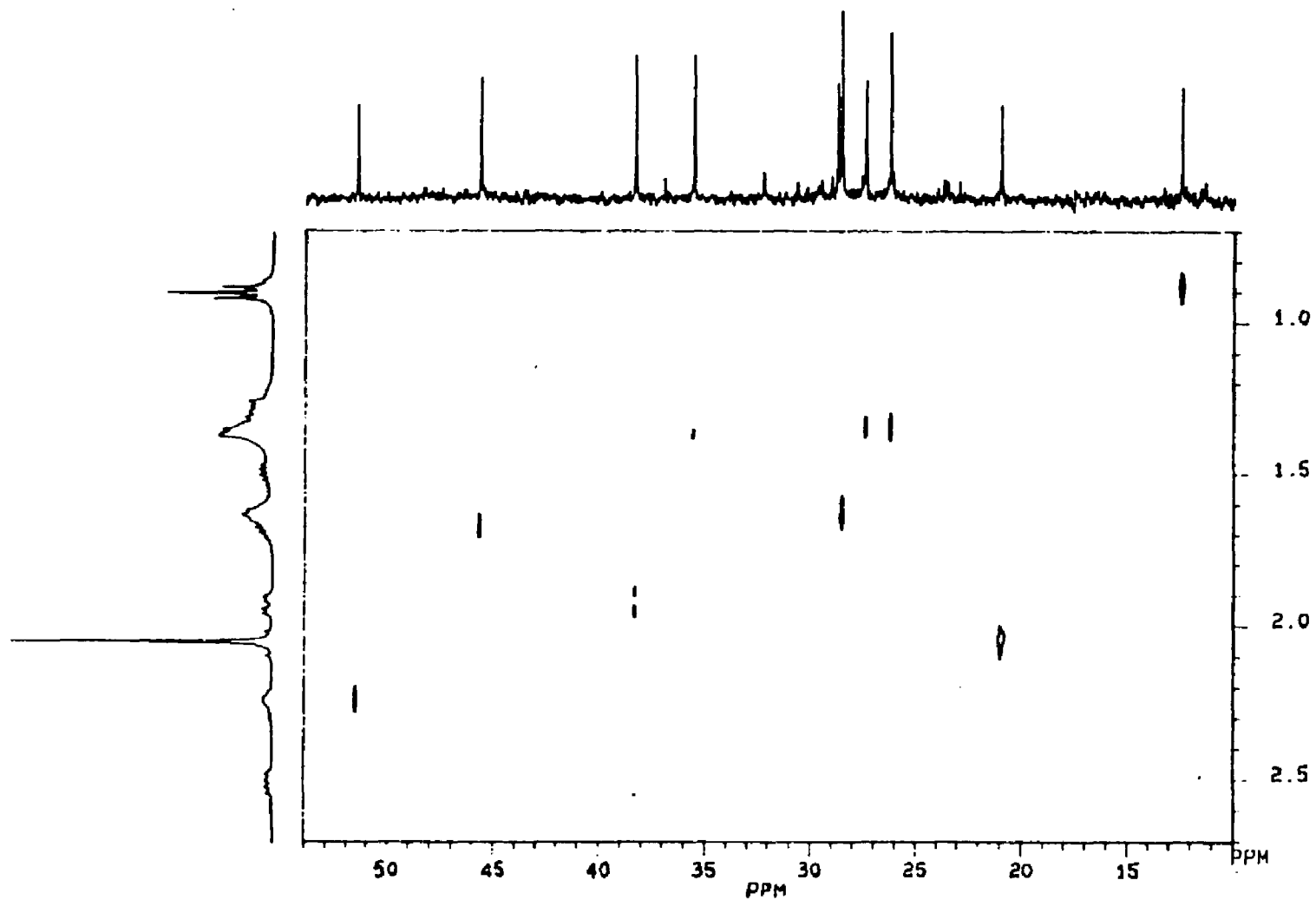
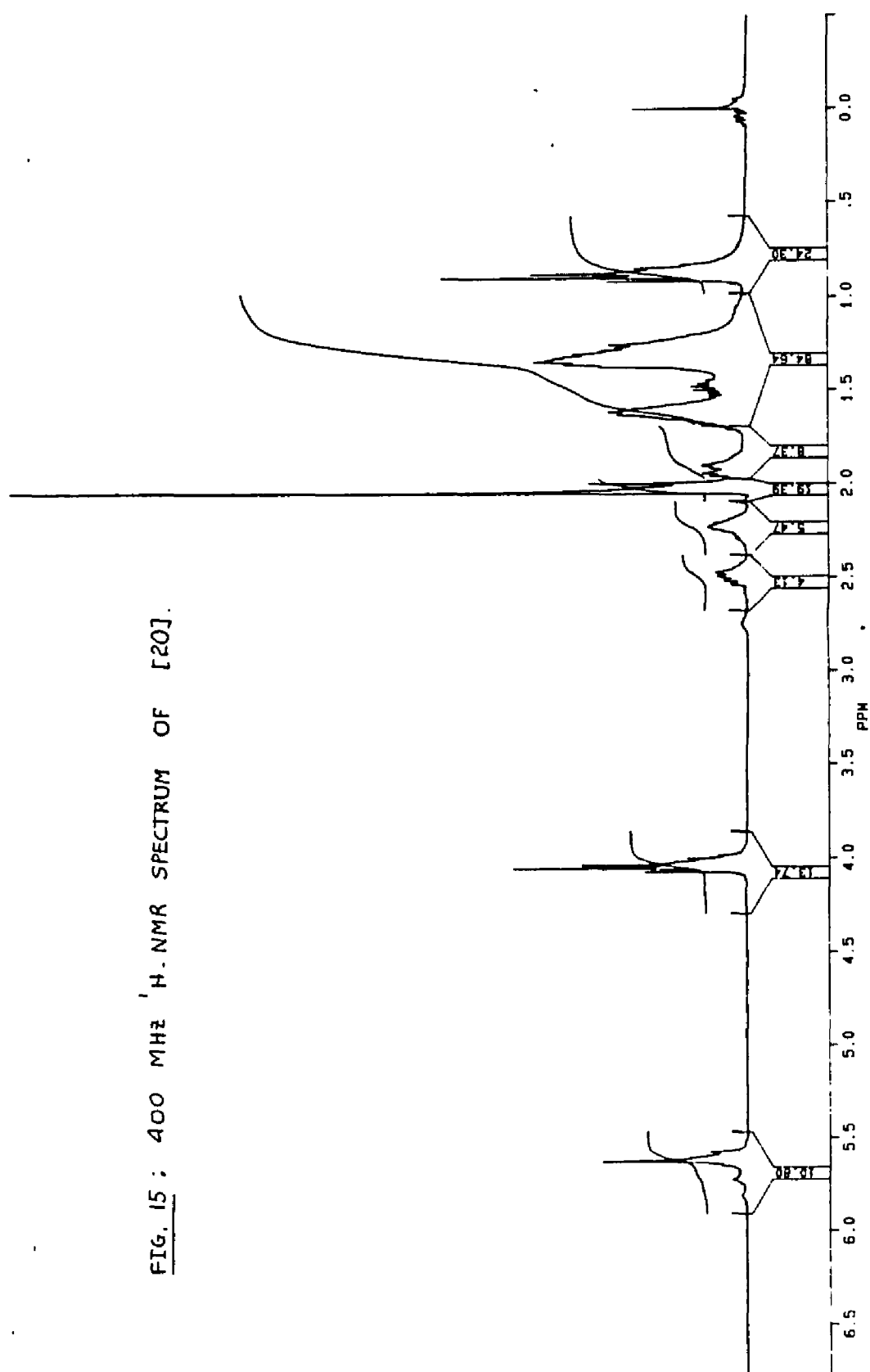


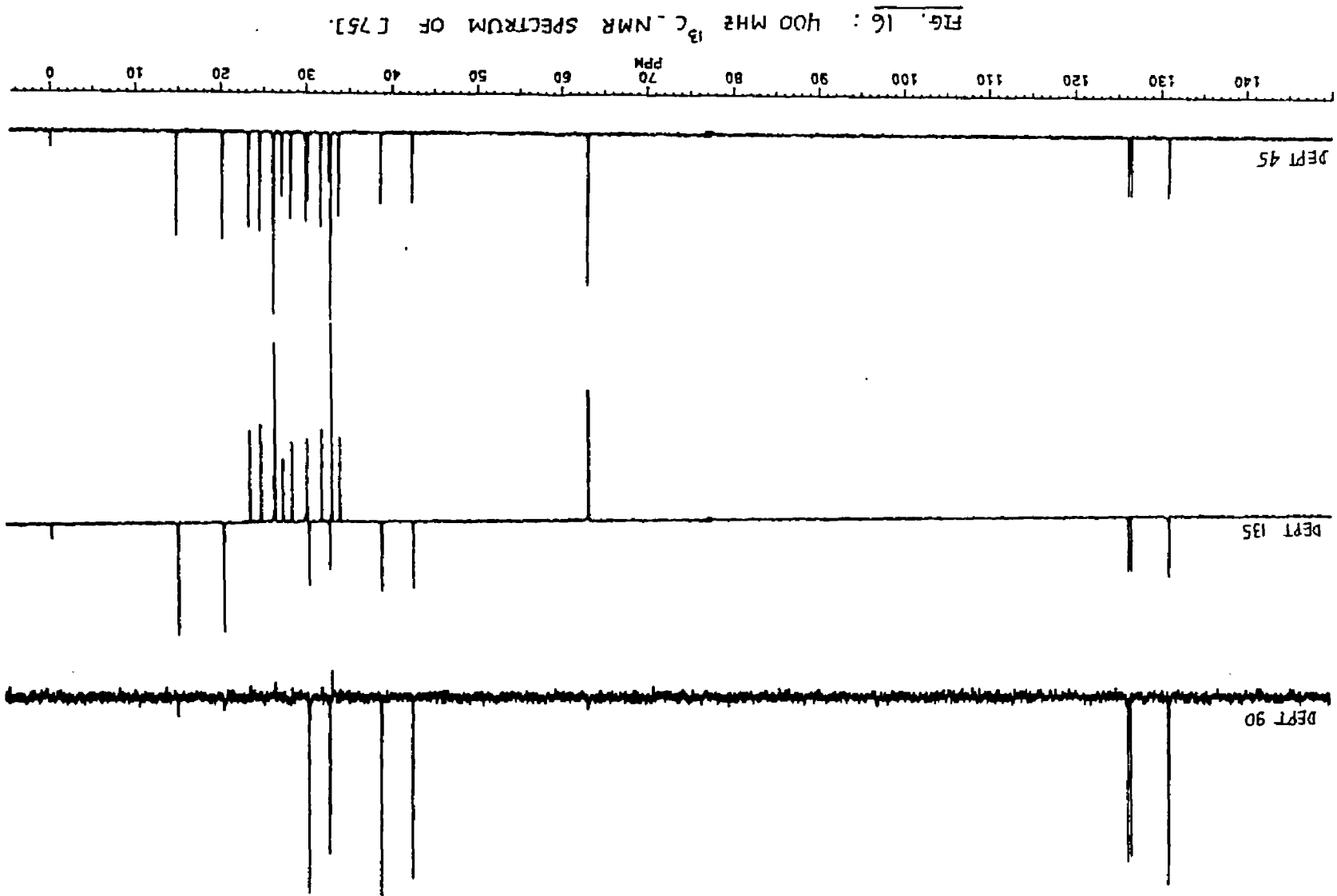
FIG. 14A. ^{13}C - ^1H SHIFT CORRELATION SPECTRUM OF [20].

nals of CH group cannot be resolved) which were correlated to ^{13}C - ^1H shift correlation spectrum of [20] (Fig. 14 A) to give chemical shifts of CH protons for the major isomer of [20] at 1.66 and 2.23 ppm, respectively. The 400 MHz ^1H -NMR spectrum (Fig. 15) of [20] showed the mixture having 2 isomers (cis and trans). The minor CH proton peaks were clearly resolved downfield from the major CH proton peaks at δ 1.94 and 2.49 ppm, and thus should be assigned to the cis isomer according to the correlation of Jaenicke and Boland¹⁷⁷.

The ^{13}C -DEPT-NMR spectrum (Fig. 16) of the mixture of [75] isomers showed 4 CH signals at δ 31.6, 38.7 ppm (for the major isomer) and 30.10, 32.90 (for the minor isomer); and 2 CH_2 peaks at δ 14.7 (minor) and 20.1 ppm (major). These chemical shifts of 4 CH carbon peaks were correlated to ^{13}C - ^1H shift correlation spectrum (Fig. 17) of [75] to 4 CH proton peaks at δ 1.38, 1.88 ppm (for the major isomer) and δ 1.68, 2.07 ppm (for the minor isomer). Application of Jaenicke and Boland's correlation in the stereochemical assignment of [75] leads to the identification of the methine protons of (i) trans-[75] as those which absorb at δ 1.38 and 1.88, and the analogous absorptions of cis-[75] as those at δ 1.68 and 2.07 (ii) trans-[20] as those which absorb at δ 1.66 and 2.23 and the analogous absorptions of cis-[20] as those at δ 1.94 and 2.49. Table 5 summarizes these chemical shifts of tertiary protons on cis- and trans-multifidens, [75],

FIG. 15 : 400 MHz ^1H -NMR SPECTRUM OF [20].





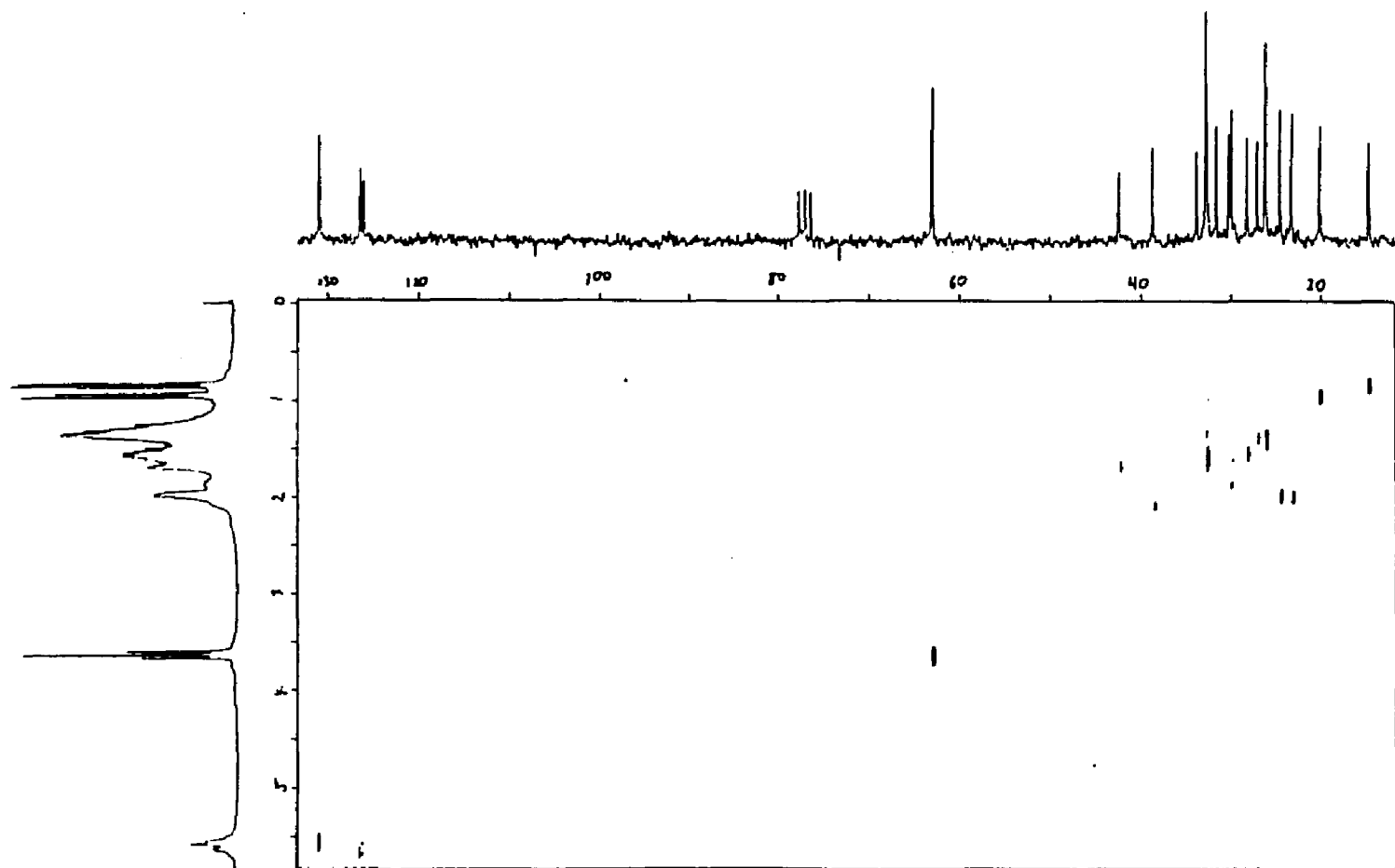
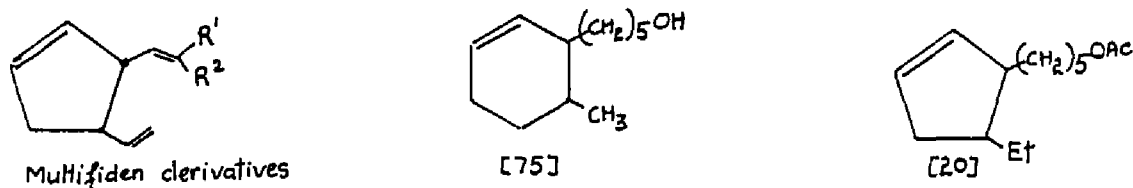


FIG. 17: ^{13}C - ^1H SHIFT CORRELATION SPECTRUM OF [75] (200 MHz).

and [20].

Table 5.



Compound	δ , CH protons (ppm)		Stereochemistry
Multifiden	2.9	3.6	CIS
	2.6	3.3	TRANS
[75]	1.68	2.07	CIS
	1.38	1.88	TRANS
[20]	1.94	2.49	CIS
	1.66	2.23	TRANS

The stereochemical assignment for [75] was further confirmed by analysis of ^1H and ^{13}C -NMR spectra. As in its starting material [63], methyl proton and methyl carbon signals of cis-[75] were at higher field (0.85 and 14.7, respectively) compared to those of trans-[46] (δ 0.96 and 20.1, respectively), which is expected based on the earlier discussion of stereochemical assignment for [63].

The assignments of major and minor isomers in [75] and [20] lead to conclusion that the silyl enol ether - hydroboration reaction used to prepare the alkenes from the corresponding ketones preserved the stereochemical relationship between substituents at C2 and C3 in the

ketone. This retention of stereochemical relationship should probably be expected because the silyl enol ether formation was carried out under conditions of kinetic control.

D. Stereochemical assignment for [18] and [19].

The relationship between the vicinal coupling constant (J) and the dihedral angle between the protons is described by Karplus equation^{170a}. One of the most important consequences of the Karplus equation is that the magnitude of coupling constants can lead to the prediction of stereochemical assignment in 1,2 disubstituted cyclohexane systems. However, in cyclopentane rings, vicinal proton coupling constants for cis and trans derivatives are very similar, and the stereochemical relationship of substituents on adjacent carbons cannot readily be evaluated from coupling constant data^{170a}. Thus the stereochemical assignment of [18] cannot be made. These substituents in [18] are in the thermodynamically more stable trans configuration based on MM2 calculation in 1,2-diethylcyclopentane which will be discussed later.

The assignment of stereochemistry in the mixture of [19] isomers was established by 400 MHz ¹H and ¹³C-DEPT NMR studies. The ¹³C-NMR spectrum of [19] showed one set of 13 aliphatic signals (20.3, 20.99, 25.88, 26.23, 26.58, 26.67, 26.95, 31.79, 33.42, 35.91, 36.94, 43.84, 64.66 ppm) and 1 carbonyl carbon signal (171.24 ppm).

Additional minor signals (13.82, 22.13, 25.15, 26.39, 32.18, 39.82) were also present. The spectral data indicated that [19] was a mixture of trans and cis isomers. The DEPT (Fig. 18) method at 400 MHz identified carbon chemical shifts of (i) CH_3 groups at 13.82, 20.30, 20.99 ppm (ii) CH_2 groups at 22.13, 25.15, 26.39, 26.23, 26.58, 26.57, 26.95, 31.79, 33.42, 35.91, 64.66 ppm (iii) CH groups at 32.18, 39.82 (for the minor isomer [19]) and 36.94, 43.84 ppm (for the major isomer of [19]). Based on a comparison of carbon chemical shifts in cis- and trans-1,2-dimethylcyclohexane¹⁷⁹ to those in [19], led to the assignments of the methyl carbon and the two tertiary carbons at δ 20.3, 36.9 and 43.8 to trans [19]. In contrast, the methyl carbon and two tertiary carbons in cis [19] were relatively shielded and located at δ 13.8, 32.2 and 39.8 ppm.

These are all reasonable expectation based on the fact that the cis-isomer will exist as a mixture of axial, equatorial conformations, whereas the trans isomer will be exclusively di-equatorial. The cis-isomer will thus show a large γ -effect. In line with this agreement, the protons attached to the ring methyl in the cis-isomer appear up-field (δ 0.82) from those in the trans-isomer (δ 0.88). It is also worth noting that in the series of compounds generated here, as well as in a few literature examples, when the 1,2-substituents are cis to one another, $J_{\text{Hc-H}}$ between the methyl protons and the ring proton is larger

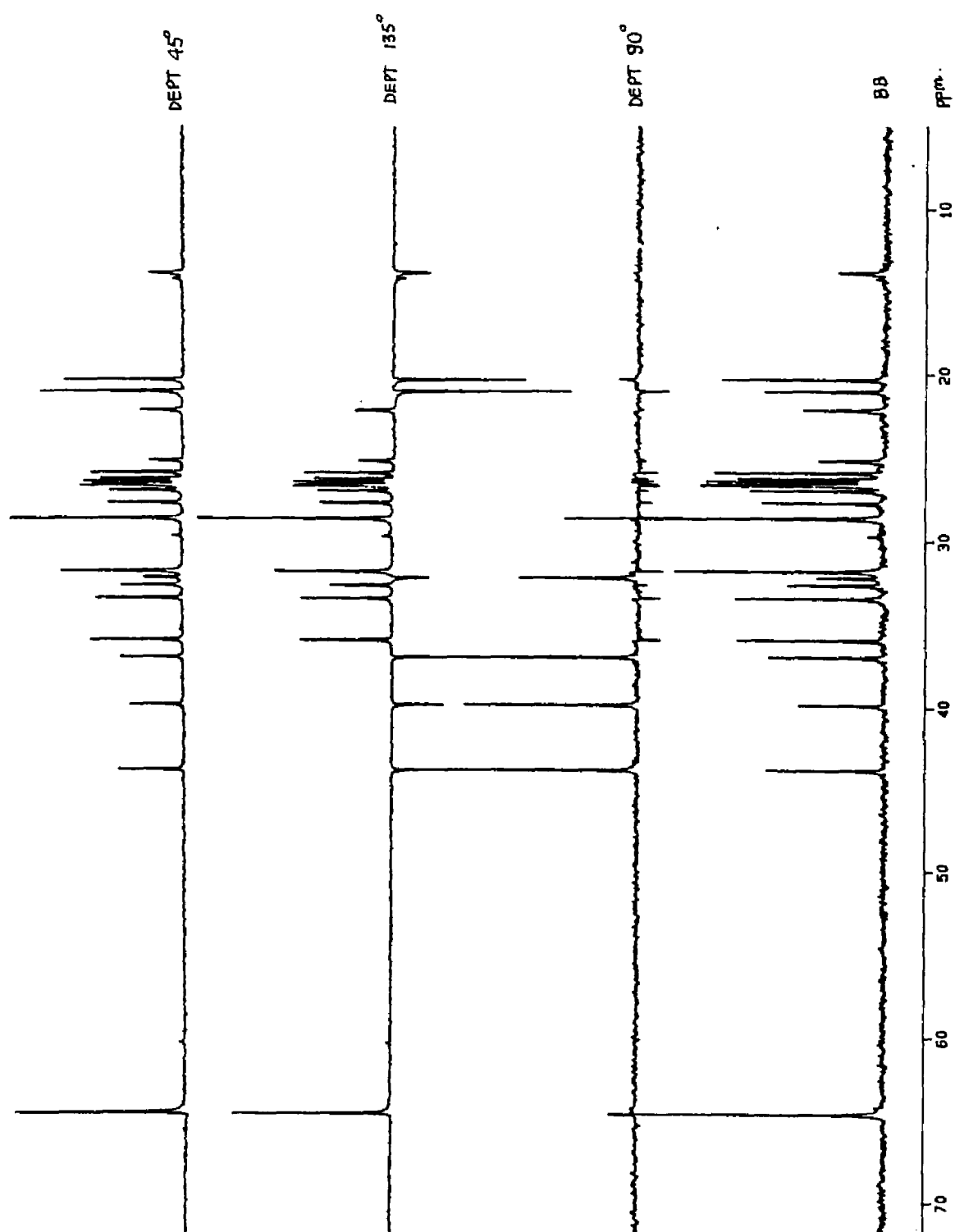


FIG. 18: ^{13}C -DEPT-NMR SPECTRUM OF [19] IN 400 MHz.

(7.12 Hz in [19] than when the substituents are trans (6.45 Hz in [19]. These methyl coupling constant and chemical shift values are almost identical to those in [63] and [21].

The stereochemical assignment for [19] was further reinforced by J_{CH-CH} coupling constant. The 400 MHz 1H NMR spectrum of [19] showed the two methine protons at δ 1.7353 and 1.7631 for the major isomer and at δ 1.5390 and 1.5488 for the minor isomer. (The chemical shift assignments were based on analogy with literature data for cyclohexane derivatives^{17ab,c}). The figures 0.0278 and 0.0098 ppm from the subtraction of 2 pairs 1.7631, 1.7353 and 1.5488, 1.5390 were multiplied by 400 (since the 400 MHz NMR spectrum was used) to give the C_1H-C_2H coupling constants, 11 Hz for the major isomer and 4 Hz for the minor isomer. The value 11 Hz is in the region characteristic of trans-1,2-dialkylcyclohexanes but too large for a cis counterparts^{17ab}. The isomer [19] which had J_{CH-CH} value about 11 Hz was assigned to be trans-[19] and the other with J_{CH-CH} value about 4 Hz was determined to have cis-configuration.

V. MM2 CALCULATIONS OF CONFORMATIONAL ENERGIES OF
CYCLOPENTANE, CYCLOPENTENE, CYCLOHEXANE, AND
CYCLOHEXENE DERIVATIVES.

In order to clarify the conformational structures of the pheromone analogs synthesized [18-21], molecular mechanics calculations (Allinger's MM2 program)¹⁷⁹ for the models (1,2-diethylcyclopentane [78]; 3,4-diethylcyclopentene [79]; 2-ethylmethylcyclohexane [80]; and 3-ethyl-4-methylcyclohexane [81]) were carried out. General principles about conformations of 1,2 disubstituted cycloalkanes (5- and 6-membered ring¹⁸⁰), cyclohexene and cyclopentene are outlined here. The results for the conformational energies of the models are also described.

1. General principles: Like cyclohexane and monosubstituted cyclohexanes, disubstituted cyclohexanes exist in chair conformations. In addition, 1,2-disubstituted cyclohexanes exist in cis and trans configurations. The trans isomer (dl pair) is either diequatorial (e,e) or diaxial (a,a) with the diequatorial conformation predominating by far except in very unusual circumstances. The cis isomer is either equatorial-axial or axial-equatorial. When the two substituents are different, the conformation in which the larger substituent is equatorial will be predominant, and the compound is potentially resolvable. When the two

substituent are the same and cis (but not trans), the two conformational isomers are mirror images of each other. In this case one is dealing with a rapidly interconverting, non-resolvable dl pair¹⁸¹. It might be noted that, for 1,2-disubstituted cyclohexanes the trans isomer (e,e) is more stable than the cis (e,a) because of the greater number of equatorial substituents.

Cyclopentane is a flexible molecule. It has been shown that two of the possible conformations¹⁸² (the half chair and the envelope) are more stable than the others. In cyclopentane itself, there is little if any energy difference between the two conformations. The molecule is thus in a rapid state of conformational flux through what is known as "pseudorotation"¹⁸³. In the course of this pseudorotation the internal energy of cyclopentane changes little (by less than 6.0 cal/mole at room temperature)¹⁸⁰, so that, unlike in the chair form of cyclohexane, no definite energy minima (corresponding to stable conformations) and maxima come into proof. The situation may change in substituted cyclopentanes. There is evidence that certain substituted cyclopentanes exist preferentially with a geometry close to either the half-chair or envelope form, which thus correspond to real energy wells or stable conformations, similar to the equatorially and axially substituted chair forms in cyclohexane. It appears¹⁸⁴ that the stable conformation of methylcyclopentane is an envelope form in which the methyl group occupies an "equatorial"

position at the tip of the envelope; in this form there is a minimum of eclipsing. A more convincing example of envelope conformation is presented by the 1,2-dimethylcyclopentanes. The trans isomer is the thermochemically more stable by 1.71 kcal/mole¹⁸⁰, which is only a little less than the corresponding difference for the cyclohexane analogs (1.87 kcal/mole)¹⁸⁰.

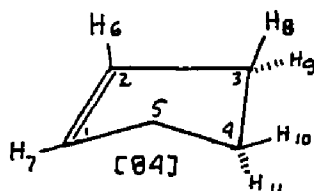
In general, the conformational aspects of cyclohexene and cyclopentene have not been explored so extensively as one might hope. The conformation of cyclohexene is that of a flattened chair or half-chair¹⁸⁰. It might be noted that, in the half-chair form, cyclohexene is a chiral molecule, but chair inversion readily converts one enantiomer to the other, the situation being similar to that in cis-1,2-dimethylcyclohexane. The cis (e',a or a',e) and trans (e,e') isomers of 3-cyclohexene-1,2-dicarboxylic acid are known¹⁸⁵. The cis is converted to the trans by base.

Models suggest that cyclopentene is more strained than cyclohexene. Nevertheless, hydrogenation of cyclopentene¹⁸⁶ is 1.66 kcal/mole less exothermic than hydrogenation of cyclohexene. Clearly the greater angle strain in the cyclopentenenes is more than offset by the greater residual eclipsing strain in the cyclopentane hydrogenation products.

2. Results for the conformational energies of the models: The steric energies of the models were calculated

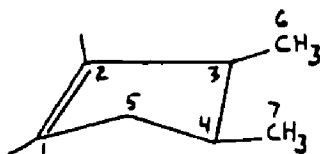
using the MM2 program of Allinger¹⁷⁹ which is based on a force field method. The MM2 program apportions the total energy into classical compression, bending, stretch-bend, van der Waals, torsional and dipole energies. The form of the equations used to calculate these energy components can be found in the reference above. The results reported here have used the built-in parameters for cycloalkenes and cycloalkanes in the QCPE release of the program to calculate the steric energies in [78-81].

From a particular set of input coordinates the MM2 program does not in general rapidly find a global minimum energy structure, but rather the nearest local minimum. One can arrive at a global minimum conformation using MM2 in several ways, which is illustrated with [79] in the following discussion. The task is to generate structural parameters for the most stable conformation of the molecule. Envelope conformers of cyclopentene and substituted cyclopentanes having C_s symmetry are known to be more stable than half-chair conformers¹⁸⁷, and one can start immediately with atomic coordinates derived by making a reasonable guess at bond angle and dihedral values, using for instance values for cyclopentene [84]. Once coordinates are supplied the program can be asked to minimize, but specifying that C_s symmetry be retained.

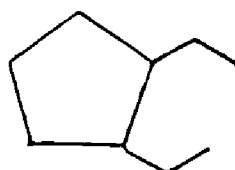


The ring system [84] is of course a simple example for applying a systematic approach to finding the global minimum. Calculations on the cis- and trans-isomer of 3,4-dimethylcyclopentene starting with the coordinates for the minimized C_s structure of [84] and substituting methyl cis (or trans) to one another on C3 and C4, then carrying out the minimization, results in a structure with a total steric energy almost 1.15 kcal/mole greater than that for the overall minimum conformer of cis-3,4-Me₂-[84] and 1.04 kcal/mole greater than that for the overall minimum conformer of trans-3,4-Me₂-[84]. The latter conformers (cis- and trans-isomer with minimum energy for each) were found using alternative sets of input coordinates.

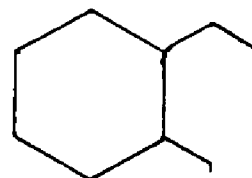
In a manner similar to the above calculations, minimum energy conformer of cis- and trans-3,4-diethylcyclopentene [79] were found starting with the coordinates for the minimized C_s structures of cis- and trans-3,4-Me₂-[84] and substituting methyls for hydrogens on



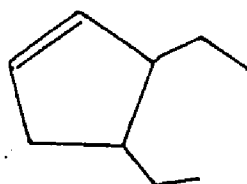
C6 and C7, then carrying out the minimization for each isomer. None of the conformers generated by the 9 pathways is exactly identical to any of the others, but they converge on a lowest energy form. For cis-[79] the 9 different minimization pathways give conformers differing by as much as 5.0 kcal/mol, and by 2.7 kcal/mol for trans-[79]. In effect, the process involves postulating input data close to local minima and surveying all local minima to assure that the lowest energy calculated structures are global minima. The results for the steric energies of the models below from MM2 calculation are reported next



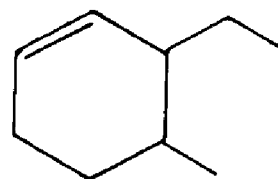
[78]



[80]



[79]

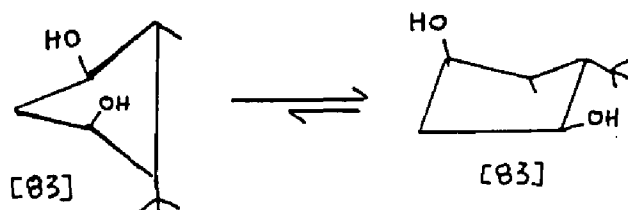


[81]

a. 1,2-diethylcyclopentane [78]:

Conformational energies of 1,2-diethylcyclopentane which were calculated from MM2 indicate that the envelope form is favored in accord with the observation of De Clercq, Brutcher and Pitzer¹⁸⁸⁻¹⁹⁰. Pitzer and Donath¹⁸⁸ found that the envelope was slightly more stable than the half-chair by 0.53 kcal/mol at the equilibrium position for cyclopentane itself, although cyclopentane is characterized by full pseudorotation. Brutcher and Bauer¹⁸⁹ discovered in the maximally puckered models (highly substituted and ring fused cyclopentanes) that the electron correlation value for the envelope was again less than for the half-chair, but the effect is partially wiped out in the envelope by the rapid increase of bond bending strain so that the two heats of formation, 7.35 vs. 7.64 kcal/mol, are nearly equal. De Clercq¹⁹⁰ reported that there is a barrier to pseudorotation for substituted cyclopentane derivatives eg. 10 kJ/mol or 2.4 kcal/mol between the half-chair [82] and the more-favored envelope form [83].

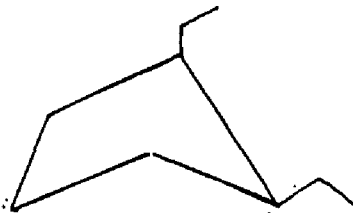

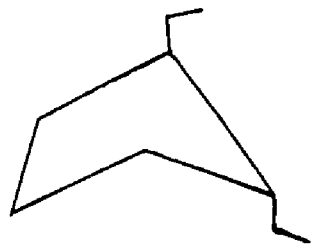
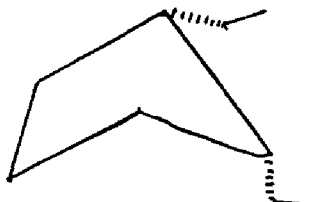
The results for the steric energy calculations on [78] are listed in Table 6. The most stable conformer of [78] is that with the two ethyl groups in



"equatorial" positions, and is the trans isomer. The conformational energy difference between diequatorial and diaxial in the trans isomer of [78] is about 1.16 kcal/mol. The cis isomers are less stable than the trans isomers. For the cis isomer of [78], the conformer with the axial ethyl group at the tip of the envelope is favored over the one with equatorial at the same position by about 0.35 kcal/mol. The energy difference between the most stable conformer of the cis and trans isomers of [78] is 2.2 kcal/mol. Fuchs¹⁹¹ has reported the thermodynamic parameters for the base catalyzed cis-trans equilibria of a series of dialkyl cyclopentane-1,3-dicarboxylates, and concluded that the positive entropy differences found for the equilibria cis \rightleftharpoons trans (2.4 J/mol.K or 0.5 cal/mol.K) apparently originate in a more variegated conformational population of the trans-isomer due to less restricted pseudorotation. The difference in entropy-of-mixing terms between cis- and trans-1,3-dimethylcyclopentane computed by De Clercq¹⁹⁰ is 2 J/mol.K in accord with the above interpretation. In 1,2-dialkylcyclopentanes the trans isomers appear to be thermodynamically preferred. Thus for cis \rightleftharpoons trans-1,2-dimethylcyclopentane, ΔG° lies in the range -1.71 to -1.94 kcal/mol¹⁹². The same trend has been found for the 1,2-dicarbomethoxy and 1,2-diphenylcyclopentanes¹⁹². There is little doubt that this preference for the 1,2-trans geometry stems from vicinal steric interfe-

rence of substituents and not from ring conformational effects¹⁹².

Table 6.

<u>Entry</u>	<u>Compound</u>	<u>Steric energy</u> (Kcal/mol)
1.		17.10
2.		14.53
3.		15.69
4.		16.74

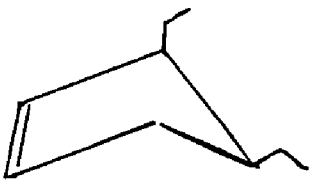

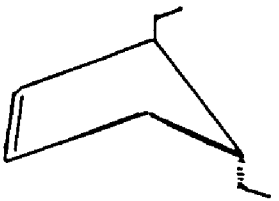

b. 3,4-diethylcyclopentene [79]:

The calculational results for [79] are shown in Table 7. As with 1,2-diethylcyclopentane, 3,4-diethylcyclopentene has the envelope form as the more stable. The trans isomer with diequatorial ethyl groups has the lowest energy (11.54 kcal/mol) and the cis isomer with an axial ethyl group at the 4-position has the highest energy (14.77 kcal/mol). The energy difference between the most stable conformers of cis and trans is about 0.95 kcal/mol. For the cis isomer, the more stable conformation (12.49 kcal/mol) preferred an equatorial ethyl group over an axial one (14.77 kcal/mol) at the tip of the envelope, unlike the corresponding 1,2-diethylcyclopentane in which the more stable conformer has an axial ethyl. It is worth noting that all trans isomers are not more stable than all cis ones, as opposed to the case of 1,2-diethylcyclopentane.

The fact that equatorial substituents are preferred over axial ones was reported by Toromanoff¹⁹³. For mono substituted cyclopentenes, it appears that the envelope conformer with the equatorial substituent is the more stable whether the substituent is at position 3 or 4, and the larger the substituent, the larger the conformer population. Similarly, relative stability relationships also hold for disubstituted cyclopentenes: for trans disubstituted derivatives, usually the envelope with two diequatorial substituents is the more stable; for cis disubs-

tituted cyclopentenenes, the more stable of the two envelope conformers is the one with the larger substituent in the equatorial orientation.

Table 7.

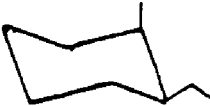



<u>Entry</u>	<u>Compound</u>	<u>Steric energy</u> (Kcal/mol)
1.		12.49
2.		11.54
3.		12.92
4.		14.77

c. 2-ethylmethylcyclohexane [80]:

The calculational results for [80] are shown

in Table B. For the cyclohexane the chair conformation is known to be most favorable. The lowest steric energy is that for the trans isomer with 2 alkyl groups in equatorial positions (10.54 kcal/mol). In contrast, when 2 substituents are in axial positions, the trans isomer gives the highest steric energy (12.72 kcal/mol). In comparing the 2 conformers of the cis isomer, the one in which the ethyl group is at an equatorial position is more stable than the one having the axial ethyl by 0.46 kcal/mol. The difference between the lowest energy cis





Table B.

<u>Entry</u>	<u>Compound</u>	<u>Steric energy</u> (Kcal/mol)
1.		11.56
2.		12.72
3.		10.54
4.		12.01

isomer and the lowest energy trans isomer is about 1.02 kcal/mol. Generally the stability order in 2-ethylmethylcyclohexane is in agreement with the well known trends in 1,2-dimethylcyclohexane.

d. 3-ethyl-4-methylcyclohexene [81]:

Table 9 summarizes the results for the conformational energies of [81]. The preferred conformation of the cyclohexene ring is a half-chair form. As with 2-ethylmethylcy-

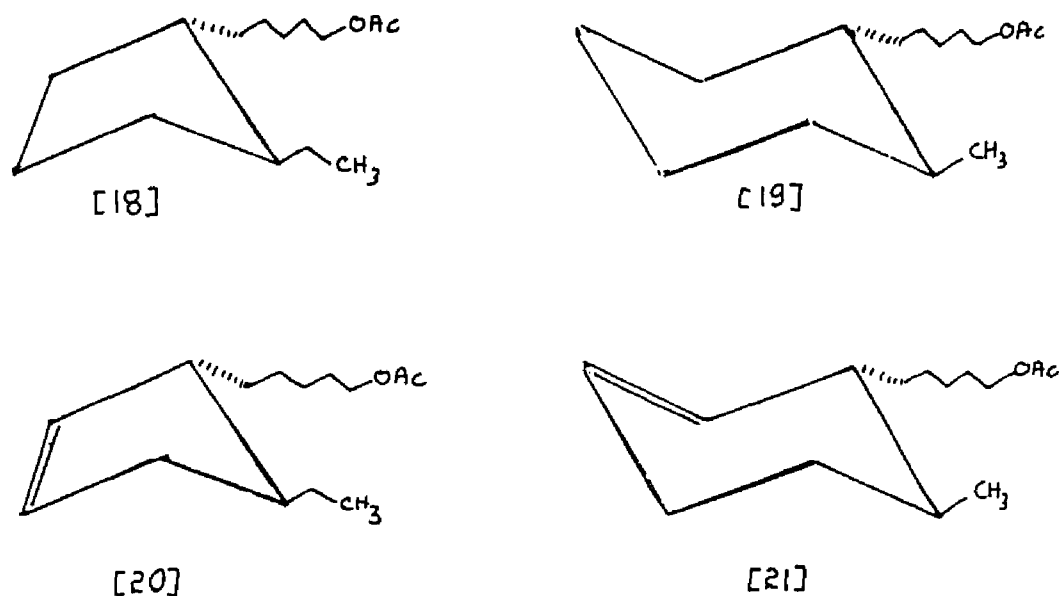
Table 9.		
<u>Entry</u>	<u>Compound</u>	<u>Steric energy</u> (Kcal/mol)
1.		9.29
2.		9.09
3.		8.50
4.		8.97

cyclohexane the most stable conformer of the trans isomer

has 2 alkyl groups in equatorial positions (8.51 kcal/mol) and this conformer is 0.58 kcal/mol more stable than the trans isomer with diaxial alkyl groups. In the 2 conformers of the cis isomer, the one in which ethyl is in an axial position shows a lower conformational energy (8.97 kcal/mol) than the one having an equatorial ethyl (9.29 kcal/mol). In contrast to the cyclohexane case, the trans diaxial isomer of the cyclohexene is not the least stable conformer.

e. Conclusion: The results for the conformational energies of the models [78-81] from MM2 calculations

Fig. 19.



show that trans isomer which has diequatorial substituents

is the most stable for all case. The pheromone analogs synthesized [18-21] in the present work have all obtained as mixtures in which the trans isomer is the major isomer. The results from MM2 calculations of the analogs suggest the most stable conformers of the pheromone analogs are those shown in Fig. 19.

The cycloalkenes prepared in this work are close analogs of the natural pheromone of the cabbage looper moth. The analogs prepared will have conformations quite different from the preferred one of the natural pheromone, which is an extended chain. Nevertheless, the molecular mechanics calculations indicate that the cyclic analogs, which having much less conformational freedom than the acyclic pheromone, will not have fixed conformations. In the case of the cyclopentene analogs, the calculations indicate that there are two quite different ring conformers for the trans isomer (ax,ax and eq,eq) that differ in energy by only about 1.5 kcal/mol. The corresponding cis isomer shows a somewhat greater preference (2.3 kcal/mol) for one conformer over the next most stable one. In the cyclohexene series the energy differences are even less. Hence, both the cyclopentene and cyclohexene pheromone analogs must be considered to represent conformationally mobile systems, albeit much more conformationally restricted than the open-chain pheromone itself.

CHAPTER III: EXPERIMENTAL.

GENERAL PROCEDURE.

Unless otherwise stated, all lithium and organocopper reagents were prepared in three-necked round-bottomed flasks. The glassware was oven dried, assembled hot, and flushed with nitrogen prior to conducting the reaction under a nitrogen atmosphere. Tetrahydrofuran (THF) was dried by distilling from Na/Benzophenone. Hexamethylphosphoramide (HMPA), DMF, Et₃N were dried by distilling from calcium hydride. Chloroform, sulfolane were dried by shaking with Linde 4A molecular sieves. Commercial anhydrous ether was used as supplied.

In general infrared spectra were recorded on either a Perkin Elmer IR-137 or IR-621 grating spectrometer as neat liquid films. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker AC-100 FT. spectrometer (unless otherwise stated) with an unregulated probe temperature of about 297°K. The spectra were recorded in CDCl₃ solution and chemical shifts are reported in part per million () downfield from TMS internal standard. ¹³C NMR, DEPT, 2D NMR spectra were obtained on either Bruker WP-200 FT or AM-400 FT spectrometers.

Mass spectra were obtained on a Hewlett Packard 5985 GC/MS, operating at 70 eV using a 30 mm x 0.25 mm ID x 0.2 film OV-1-B.P., fused silica capillary column and are

reported as m/e (relative abundance) (unless otherwise stated). The precise mass measurements were obtained from the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee and Micanal Laboratories, Tucson, Arizona.

Boiling points were obtained at atmospheric pressure, unless otherwise stated, and are uncorrected. All temperatures are reported in degree centigrade.

1. Preparation of cyclopentanone ethylene ketal [31]:

A 3 L round-bottomed flask was charged with cyclopentanone (424.4 mL, 4.8 mol), 1,2-ethanediol (328 g, 5.28 mol), 1 L of reagent grade benzene and 200 mg of *p*-toluenesulfonic acid monohydrate. The flask was attached to a water separator under a reflux condenser fitted with a drying tube. The reaction mixture was continuously refluxed for one week (95 mL of water was collected in the trap). It was cooled to room temperature, extracted successively with 800 mL of 10% NaOH solution and 5 x 400 mL portions of water, dried over anhydrous K_2CO_3 , and distilled through a 20 cm Vigreux column under reduced pressure. 1,2-dioxaspiro[4.4]nonane [31] was obtained as a colorless liquid with a pleasant odor, bp 70-72°C/17 mm, (lit.¹⁹⁴ bp 150-155°C), yield 464 g (76%).

1H NMR ($CDCl_3$, TMS): 1.60 (s, 4 H, -O-CH₂-CH₂-O)

3.72 (s, 8 H, -CH₂-CH₂-CH₂-CH₂-); MS, m/e (rel intensity): 128(M⁺, 12), 100(14), 99(100), 97(7), 53(3).

2. Preparation of 2-Bromocyclopentanone ethylene ketal [32]:

Following the general procedure of Garbisch⁹⁰ a solution of freshly distilled [31] (10.3 g, 0.8 mmol) in 1 L of freshly distilled ethylene glycol was prepared in a 2 L three-necked round-bottomed flask equipped with a

dropping funnel, a condenser to which a drying tube was connected, a mechanical stirrer, and a thermometer. To the stirred solution at room temperature was added a small portion of Br_2 . After 2 min, uptake of the Br_2 was not complete, and the solution was warmed up by a hot tap-water bath until the reaction was initiated (Br_2 was consumed very fast, and the reaction temperature went up to 30°C from 24°C). The remainder of the Br_2 (41.2 mL, 0.80 mol) was added at $15\text{--}20^\circ\text{C}$ at such a rate so as to maintain a faint coloration (slight yellow) of Br_2 at all times (an ice cold water bath was used to control the reaction temperature). At the end of the addition the Br_2 color did not persist for more than 2 min at 10°C , and additional Br_2 (2 mL) was added to realize this condition. The cool reaction mixture, which turned colorless after 3 min, was slowly poured into a stirred mixture of 200 g of anhydrous Na_2CO_3 and 800 mL of pentane, and CO_2 gas was evolved. After continuing to stir for 10 more min, 1 L of water was added, the combined pentane extracts of 2 extractions was dried with anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure (rotavapor) to give a colorless liquid [32] boiling at $96\text{--}98^\circ\text{C}/15\text{ mm}$, (lit⁹² bp $95\text{--}100^\circ\text{C}/15\text{ mm}$), yield 153.5 g (93%).

^1H NMR (CDCl_3 , TMS):

1.50–2.50 (m, 6 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$), 4.15 (m, 5 H,

-O-CH₂-CH₂-O-C-CH-Br). MS, m/e (rel intensity):

208(M⁺, 4), 206(4), 179(7), 177(7), 100(14), 99(100),
55(10).

3. Dehydrobromination of 2-Bromocyclopentanone ethylene ketal:

KOH (120.4 g, 2.15 mol) was dissolved in 240 mL of diethylene glycol (previously dried over 4 Å molecular sieves) by stirring and heating for 45 min. The very dark brown solution was cooled to room temperature by means of an ice water bath. [32] (153.5 g, 0.742 mol) was added dropwise to the cooled, dark brown alkaline solution over 40 min. Then a pinch of NH₄Cl was added, and the mixture was heated to reflux under N₂ for 2 h. At the beginning of the reflux there was a very viscous brown liquid containing solid KBr. More and more KBr separated later. At the end of the reflux a dark brown suspension was obtained. The reaction mixture was cooled to room temperature under N₂ with stirring for 9 h. On distillation, the portion coming over up to 110°C/12 mm was collected. It contained 2 layers of colorless liquid. The bottom layer, which was diethylene glycol (d = 1.118), was discarded. The top layer (cyclopentenone ethylene ketal [33], d = 1.067) was dried over K₂CO₃ and redistilled to give pure [33], bp 61-62°C at 11 mm (lit.⁷⁹ bp 55°C/11 mm), yield 74.2 g (79.4%). ¹H NMR (CDCl₃, TMS): 2.00-2.60 (m, 4 H,

-C-CH₂-CH₂-C=), 4.00 (s, 4 H, -O-CH₂-CH₂-O-), 5.50-5.80 (m, 1 H, -C-C=CH-CO), 6.00- 6.20 (m, 1 H, -C-CH=C-CO). MS, m/e (rel intensity): 126(M⁺, 100), 125(18), 99(42), 96(18), 83(10), 82(39), 81(26), 67(15), 66(18), 65(9), 55(13), 54(16), 53(12).

4. Hydrolysis of cyclopentenone ethylene ketal:

Following the procedure of Wanzlick ⁷⁹ with some modification, to 74.2 g (0.589 mol) of [33] in a 200 mL one necked round-bottomed flask was added with swirling 12 mL of a 10% aqueous oxalic acid solution in one portion. The reaction mixture was then cooled with an ice-cold water bath for several minutes. The slightly yellow reaction mixture became homogeneous as heat evolved on mixing. After stirring for 3 h at room temperature, the yellow color of the solution faded gradually, and the unpleasant smell of starting material was gone. A pinch of NaHCO₃ (CaCO₃ was used in Wanzlick's method, however it is not as effective as NaHCO₃) was added to neutralize the solution, and the product was distilled from the glycol under vacuum to give 2-cyclopentenone [34] as a colorless liquid, bp 69-70°C/19 mm, (lit¹⁹⁵ bp 64-65°C/19 mm), yield 36.1 g (76%).

¹H NMR (CDCl₃, TMS): 2.20 (m, 2 H, -CH₂-CO-), 2.69 (m, 2 H, -CH₂-C=C-CO-), 6.09 (m, 1 H, C=CH-CO-), 7.72 (m,

1 H, -CH=C-CO-). IR (neat, cm⁻¹): 3040 (-HC=CH-), 1700 (C=O), 1590 (C=C); MS, m/e (rel intensity): 82(M⁺, 100), 81(19), 54(19), 53(15), 39(13).

5. Preparation of 3-ethyl-1-trimethylsiloxycyclopentene

[38]:

A 100 mL three-necked round-bottomed flask equipped with an Ar inlet system and a 25 mL pressure equalizing addition funnel was charged with 0.79 g (139 mmol) of Li wire containing 0.8% Na in 40 mL of anhydrous ether. EtBr (4.36 g, 40 mmol) in 12 mL of anhydrous ether was added over 30 min with magnetic stirring at -5°C. When the addition of the EtBr solution was completed the cloudy, gray slurry with some shiny metal pieces was stirred for an additional 6 h at -5°C to -10°C with cooling by means of a NaCl ice bath. At the end of the stirring most of the Li wire was used up (0.09 g of Li was left over). The reaction mixture was filtered through a glass wool plug in an inlet adapter which was attached to a 50 mL dropping funnel. This cloudy, gray solution containing EtLi in ether was then added dropwise over 20 min at -35°C to a slurry of 3.8 g (20 mmol) of purified CuI (white powder) in 20 mL of freshly distilled THF, which was stored in a 250 mL three-necked round-bottomed flask fitted with an Ar inlet system. The color of the mixture changed from

yellow to dark brown. After stirring at -35°C for 15 min the solution of [34] (1.64g, 20 mmol) in 4 mL of freshly distilled THF was added dropwise over 2 min to the dark brown reaction mixture to give a dark purple slurry. Following a 10 min period at -40°C , 5 mL of Me_3SiCl was added slowly to the reaction mixture, which turned dark green and then black. On warming to room temperature, the reaction mixture, having a black bottom layer and a clear top layer, was poured into a mixture of 200 mL of hexane, 3 mL of Et_3N and ice water. The hexane solution was separated, washed with saturated NaHCO_3 , dried over anhydrous Na_2SO_4 and concentrated in vacuo (rotavapor). Short path distillation gave a mixture of 2 isomers, [38] and [38A] (ratio 90:10 based on GC areas), bp $83^{\circ}\text{C}/9\text{ mm}$, yield 2.40 g (65%). $^1\text{H-NMR}$ for the mixture, which is presumably the spectrum of [38] (200 MHz, CDCl_3 , TMS): 0.20 (s, 9 H, Si-Me_3); 0.85 (t, $J = 7.3\text{ Hz}$, 3 H, $-\text{CH}_3$), 1.25 - 1.50 (m, 2 H, $-\text{CH}_2-\text{CH}_3$), 1.95 - 2.50 (m, 5 H, $-\text{CH}_2-\text{CH}_2-\text{CH}-$), 4.58 - 4.70 (m, 1 H, $-\text{C}=\text{CH}-$); MS, m/e (rel intensity): major isomer [38] (ret time 10.5): 184(M^+ , 12), 169(10), 155(75), 75(41), 73(100); minor isomer [38A] (ret time, 10.7): 184(M^+ , 6), 169(5), 155(100), 75(17), 73(84).

This mixture without further purification was used in procedure 7 below. Microanalysis of the mixture was

not attempted because major changes in the NMR spectrum were apparent after storage at room temperature overnight.

6. Preparation of 5-bromopentyl acetate [40]:

Following the procedure of Borowitz ¹⁹⁶⁶ with some modification, to a mixture of tetrahydropyran (334 g, 4.0 mol) and ZnCl_2 (100.8 mg) at 0 °C was added acetyl bromide (319.6 g, 2.60 mol) dropwise over 3.5 h with stirring at such a rate so as to maintain the reaction temperature. The yellow solution was stirred at 0 °C for 30 min, allowed to warm to room temperature over 1 h and 10 min, and then heated at reflux for 5 h or until the reaction temperature was at 120–130 °C. After the dark brown, hot solution cooled, CHCl_3 (1.6 L) was added, and the reaction mixture was washed with 532 mL of water, 3 x 280 mL portions of saturated NaHCO_3 solution, and 3 x 540 mL portions of water. The extract was dried over anhydrous MgSO_4 and concentrated on a rotary evaporator. The crude product was simply distilled at reduced pressure to give a colorless oily product [40], bp 95–96 °C/3 mm (lit.¹⁹⁶⁶ 90–91.5 °C/2.5 mm), yield 494.5 g (91%).

^1H NMR (CDCl_3 , TMS):

1.40–1.90 (m, 6 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$), 2.05 (s, 3 H, $-\text{OC}-\text{CH}_3$), 3.42 (t, $J = 6.1$ Hz, 2 H, $-\text{CH}_2-\text{Br}$), 4.03 (t, $J = 6.0$ Hz, 2 H, $-\text{CH}_2-\text{O}$),

IR (neat, cm^{-1}): 1735 (C=O). MS, m/e (rel intensity): 150($\text{M}^+ - \text{AcOH}$, 22), 148(22), 69(94), 61(36), 43(100).

7. Preparation of 3-ethyl-2-(5-acetoxypentyl)
cyclopentanone [37]:

A solution of the mixture of silyl enol ethers [38] and [38A] (0.92 g, 5.0 mmol) in 10 mL of anhydrous THF was added dropwise at -35°C to a milky gray suspension of lithium amide [prepared from 73 mg of Li wire, 80 mL of ammonia, 30 mL of anhydrous THF and a trace of ferric nitrate at -40 to -35°C]. The clear, brown black reaction mixture was mechanically stirred under N_2 atmosphere. After stirring for 15 min at -30°C , a solution of [40] (4.2 g, 20.0 mmol) in 5 mL of dry THF was added over a 30 sec interval. The cold bath was removed. The reaction mixture was stirred at ambient temperature for 1.5 h and quenched with 562 mg of NH_4Cl . The ammonia was evaporated under a stream of N_2 . The resulting residue was diluted with 125 mL of THF, stirred at room temperature for 2 h and 50 min, and poured into a solution of 200 mL of ice water and 40 mL of acetic acid. This solution was extracted with 3 x 200 mL portions of ether. The combined ethereal layer was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Toluene (100 mL) was added and the mixture evaporated again to remove acetic acid. The residue

was chromatographed on 200 g of silica gel, eluting with a gradient of 2-10% ethyl acetate-hexane (v/v). The solvent was removed to give a mixture of isomers (cis/trans = 56/44 by GC) of [37] as a colorless oily product, yield 0.5 g (41%). (See the results and discussion section for a discussion of stereochemical assignments.)

^1H NMR (CDCl_3 , TMS): 0.96

(t, $J = 7.0$ Hz, 3 H, $-\text{CH}_2-\text{CH}_3$), 1.14-1.81 (m, 10 H),

2.06-2.70 (m, 6 H, $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{CH}-\text{CH}-$),

2.05 (s, 3 H, $\text{OC}-\text{Me}$), 4.05 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}-$);

IR (neat, cm^{-1}): 3460 ($\text{C}=\text{O}$ overtone), 1745 ($\text{C}=\text{O}$),

1735 (OCO), 1160 ($\text{C}-\text{CO}-\text{C}$), 1280 ($\text{C}-\text{O}$).

MS, m/e (rel intensity): trans isomer (ret time 11.5 min):

240(M^+ , 0.1), 112(21), 83(100), 69(9), 67(6), 55(12),

43(15), 41(7); cis isomer (ret time 11.8 min: 240(M^+ , 3),

125(13), 113(8), 112(99), 97(14), 95(9), 84(7), 83(100),

81(11), 79(6), 70(9), 69(18), 67(13), 55(24), 43(32),

41(12).

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_3$: C, 69.96; H, 10.06;

Found: C, 69.79; H, 10.25.

B. An attempt to prepare [37] from 2-cyclopentenone via 3-ethylcyclopentanone:

A. Preparation of 3-ethylcyclopentanone [36]:

Ethyl bromide (8.68 g, 80 mmol) in 80 mL of anhydrous

ether was added dropwise at -15 to -22°C to Li wire containing 0.8% Na (1.58 g, 22.7 mmol) in 24 mL of anhydrous ether under Ar with mechanical stirring. The reaction temperature was held at -20°C for 2 h. This cold gray solution was then added to a slurry of CuI (7.6 g, 40 mmol) in 40 mL of THF at -35°C . The color of the mixture changed from yellow to dark brown, and finally to dark purple. After stirring at -35°C for 15 min a solution of [34] (3.27 g, 40 mmol) in 8 mL of anhydrous ether was added dropwise to give a dark yellow-brown slurry. Following a 10 min period at -40°C 25 mL of Me_2SiCl was added dropwise to the mixture, which turned dark green then dark purple, and finally black. The reaction mixture was warmed to 10°C , cooled to -20°C for 2 h and the cooling bath was removed. On warming to room temperature the reaction mixture was poured into a mixture of 400 mL of hexane, 5 mL of Et_3N and ice water. The hexane solution was separated, washed with saturated NaHCO_3 solution, dried over Na_2SO_4 and concentrated in vacuo. Short path distillation at 100 – $102^{\circ}\text{C}/60$ mm yielded 1.92 g (42.9%) of [36] as a colorless liquid (lit.¹⁹⁸⁰ bp $150^{\circ}\text{C}/760$ mm). ^1H NMR 200 MHz (CDCl_3 , TMS): 0.95 (t, $J = 7.0$ Hz, 3 H, $-\text{CH}_2-\text{CH}_3$), 1.50 (q, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{CH}_3$), 1.72–1.86 (m, 2 H, $\text{OC}-\text{CH}_2-\text{CH}_2-\text{CH}-$), 2.00–2.30 (m, 1 H, $-\text{C}-\text{CH}-\text{Et}$), 2.36 (d, $J = 7.5$ Hz, 2 H, $\text{OC}-\text{CH}_2-\text{CH}_2-$), 2.44 (d, $J = 4.1$ Hz, 2 H, $\text{OC}-\text{CH}_2-\text{CH}-$),

IR (neat, cm^{-1}): 1745; MS, m/e (rel intensity): 112(M^+ , 51), 84(12), 83(100), 79(4), 70(13), 69(8), 56(18), 55(27).

B. An attempt to prepare [37] from [36]:

A solution of [36] (1.44 g, 12.8 mmol), pyrrolidine (4.13 g, 27.9 mmol) and 13 mg of *p*-toluenesulfonic acid in 3.85 mL of toluene was placed in a 25 mL one-necked flask to which a Dean Stark water separator was attached. The solution was refluxed under a N_2 atmosphere for 24 h. The excess pyrrolidine and toluene were removed from the reaction mixture on a rotary evaporator. The residue was treated with [40] (1.17 g, 5.6 mmol) in toluene (2.8 mL) and heated at reflux under N_2 for 19 h. Distilled water (0.08 mL) was added and refluxing was continued for 30 min. The reaction mixture was cooled, 10% H_2SO_4 (0.08 mL) was added, and the mixture was extracted with ether several times. The combined extracts were washed with water, dried solvent was removed to give a crude product which did not contain [37] (by comparing MS of the authentic sample [37]). [36] was recovered as shown by 1H NMR and MS analysis.

9. Preparation of 5-iodopentyl acetate [40A] via

Finkelstein reaction:

A mixture of anhydrous NaI (37.5 g, 0.25 mol) and

265 mL of anhydrous acetone was heated on a steam bath for 1 h with occasional shaking in a 500 mL round-bottomed flask fitted with a reflux condenser. To the cooled colorless solution was added [40] (40.8 g, 0.19 mol) in one portion. The yellow solution with some white precipitate was heated to 58°C to 60°C for 22 h with stirring. The mixture was cooled to room temperature and filtered with suction. The inorganic salts were washed with 50 mL of acetone, and the filtrate was concentrated on a rotary evaporator. The residue was poured into 220 mL of water. The lower layer was withdrawn and washed successively with 44 mL of 10% NaHSO₃ solution, 44 mL of 10% NaHCO₃ solution and then 44 mL of water. It was dried with anhydrous MgSO₄ and distilled under reduced pressure to yield 27.2 g (55%) of [40A], bp 130–132°C/2 mm (lit. ¹⁹⁶⁶ bp 130–132°C/1.9 mm). ¹H NMR (CDCl₃, TMS): 1.30–1.90 (m, 6 H, -CH₂-CH₂-CH₂-), 2.05 (s, 3 H, OC-CH₃), 3.16 (t, J = 6.0 Hz, -CH₂-I), 4.05 (t, J = 6.0 Hz, 2 H, -O-CH₂-). IR (neat, cm⁻¹): 1742, 1246, 1036, 590; MS, m/e (rel intensity): 256 (M⁺, 10), 196(5), 155(11), 141(2), 129(20), 127(3), 87(12), 69(100), 43(13).

10. Attempt to prepare [37] from [34] in one pot:

Several drops of EtBr (50 mol) in 20.8 mL of anhydrous ether were added dropwise at room temperature to Li wire

containing 0.8% Na (0.99 g, 142.5 mmol) in 69.4 mL of anhydrous ether under Ar to initiate the reaction (cloudy solution, shiny Li pieces). The remaining EtBr was added at -10 to -5°C with mechanical stirring. The reaction temperature was held at -5 to -10°C for 2 h. This cold gray EtLi solution (-50°C) was then added to a slurry of CuI (4.9 g, 25 mmol) in 34.7 mL of anhydrous ether at -20°C . The color of the mixture changed from yellow to dark purple. After stirring at -20°C for 15 min, the solution of [34] (1.03 g, 12.5 mmol) in 12.5 mL of anhydrous ether was added dropwise over 15 min to give a dark green or dark blue mixture which was maintained at -20°C with stirring for 1 h. A solution of anhydrous THF (8.7 mL) and anhydrous HMPA (8.7 mL) was added, followed by rapid addition of excess [40A] (25.6 g, 0.1 mol). The brown-black mixture was allowed to warm to room temperature and stirred for 3.5 h. The black reaction mixture was poured into a 10% aqueous NH_4OH solution, and the organic layer was separated, washed successively with 10% NH_4OH , water, and saturated brine, and dried over MgSO_4 . Evaporation of solvent afforded no desired product [37]. Only [36] was obtained, as shown by ^1H NMR and MS analyses.

11. An attempt to prepare [37] from [38]:

Method A: A 50 mL three-necked flask was equipped with

a N₂ inlet tube with a stopcock, a glass joint fitted with a rubber septum, a 10 mL pressure-equalizing dropping funnel, a thermometer and a magnetic stirring bar. After the apparatus was dried in an oven, a catalytic amount of triphenylmethane was added to the flask and the apparatus was flushed with N₂. A static N₂ atmosphere was maintained in the reaction vessel throughout the subsequent operations involving organometallic reagent. An ethereal solution containing 1.5 M MeLi (14.06 mL, 21.1 mmol) was added to the reaction vessel from a hypodermic syringe. The ether was removed by evacuating the apparatus while the solution was stirred and the flask was warmed with a water bath (40°C). The reaction vessel was refilled with N₂ and then 21.1 mL of 1,2-dimethoxyethane was transferred to the flask. The resulting orange solution was cooled to 0–10°C and the silyl enol ether [38] (1.84 g, 10 mmol) was added dropwise with stirring. To this cold, cloudy, light pink reaction mixture [40] (5.6 g, 26.8 mmol) was added rapidly. The resulting yellow solution was stirred 3 min and then poured into 26 mL of cold, saturated aqueous NaHCO₃ and extracted with 3 x 8 mL portions of pentane. The combined organic extracts were dried over anhydrous MgSO₄ and then concentrated under reduced pressure with a rotary evaporator. The residue did not contain the desired product [37]. [40] was recovered, and [36] was formed, according to ¹H NMR and MS analysis.

Method B:

A mixture of silyl enol ether [38] (1.84 g, 10 mmol) and 1.5 M MeLi in ether (7.33 mL, 11 mmol) was stirred at 25°C for 30 min and then the ether was removed from the suspension of the lithium enolate. The light green residue was dissolved in 6.1 mL of 1,2-dimethoxyethane at 25°C and then [40] (3.14 g, 15 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and 15 min and then partitioned between pentane and 12 mL of saturated aqueous NaHCO₃. Concentration of the pentane extracts gave no desired product [37], as shown by comparison of ¹H NMR and MS spectra with those of the authentic sample. [36] was obtained, and [40] was recovered, as shown by ¹H NMR and MS analysis.

12. Preparation of 2-(5-acetoxypentyl)-2-carbomethoxycyclopentanone [42]:

5-Bromopentyl acetate [40] (146.3 g, 0.70 mol) was added dropwise to a well-stirred suspension of 2-carbomethoxycyclopentanone (100.0 g, 0.70 mol) and K₂CO₃ (193.0 g, 1.39 mol) in 2 L of anhydrous acetone. The reaction mixture was refluxed for 28 h. After filtration, the solvent was removed in vacuum and the residue was distilled to give a colorless oily product [42] at 222-223°C/4 mm (lit.¹⁹⁷ bp 155-160°C/0.6 mm), yield 127.8 g (77%).

¹H NMR (CDCl₃, TMS):

1.24-1.75 (m, 8 H), 2.04 (s, 3 H, OC-Me),

2.04-2.30 (m, 4 H, $-\text{CH}_2-\text{CH}_2-$ ring),
 2.37 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{CO}-$),
 3.71 (s, 3 H, $\text{O}-\text{CH}_3$),
 4.04 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}-$);
 IR (neat, cm^{-1}): 1748 ($\text{C}=\text{O}$), 1733 ($\text{C}=\text{O}$), 1030;
 MS, m/e (rel intensity): 270 (M^+ , 4), 238 (13),
 142 (52), 141 (18), 129 (11), 127 (10), 111 (32),
 110 (100), 109 (11), 82 (10), 69 (67), 55 (17), 43 (37),
 41 (15).

13. Preparation of 2-(5-acetoxypentyl)cyclo-
pentanone [43]:

Following the general procedure of Bernady¹⁹⁷, a clear mixture of [42] (40.4 g, 0.14 mol) in 47.3 mL of acetic acid and 63 mL of 25% HCl was refluxed for 23 h. The light yellow solution was cooled and extracted with 3 x 300 mL portions of benzene. The combined organic phase was washed with water until no trace of acid existed in the aqueous phase, and with saturated NaCl solution. The extract was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator to give crude [43] which was then distilled at $149-151^\circ\text{C}/4$ mm to yield 22.3 g (75%) of pure product (lit.^{196c} bp $115-121^\circ\text{C}/0.6$ mm).

^1H NMR (CDCl_3 , TMS): 1.67-2.00 (m, 12 H),
 2.05 (s, 3 H, $\text{OC}-\text{Me}$),
 2.10-2.44 (m, 3 H, $-\text{CH}_2-\text{CO}-\text{CH}-$),
 4.05 (t, $J = 7.0$ Hz, 2 H,

-CH₂-O-). IR (neat, cm⁻¹): 1745(C=O), 1248, 1156, 1035; MS, m/e (rel intensity): 212(M⁺, 2), 109(7), 97(12), 85(7), 84(100), 83(19), 69(20), 67(12), 55(16), 43(33), 41(14).
¹³C NMR (CDCl₃): 20.38, 22.12, 25.58, 26.78, 27.96, 28.13, 29.24, 37.65, 48.53, 63.96, 170.48, 220.27.

14. Preparation of 1-acetoxy-2-(5-acetoxypentyl)
cyclopentene [44A]:

Following the general procedure of Bernady¹⁹⁷, a light yellow solution of [43] (15.9 g, 75 mmol) and 174 mg of *p*-toluenesulfonic acid in 36.1 mL of acetic anhydride was refluxed, while the acetic acid which formed was fractionally distilled off through a glass bead-packed column. Acetic anhydride was added periodically (total 75 mL) to maintain the original volume. After 10 h as the acetic acid ceased to distill over, the dark brown mixture was heated until the boiling point (136^oC) of acetic anhydride was reached. The mixture was cooled and poured onto 72 mL of saturated NaHCO₃ solution and 60 mL of hexane. Additional solid NaHCO₃ was added cautiously until a saturated solution was maintained (solid NaHCO₃ remained in the reaction mixture, and a slow response of gas evolution was observed as NaHCO₃ was added). The mixture was stirred for 30 min until gas evolution ceased. The organic phase was washed with water, then brine, dried over anhydrous MgSO₄ and concentrated on a rotary evaporator to give 6.09 g of a dark brown oil with a pleasant odor. The oil was chroma-

tographed on 200 g of silica gel, eluting with 2% ethyl acetate-hexane (v/v), to yield 10.24 g (58%) of a colorless oil [44A] (lit.¹⁹⁷ bp 121-123°C/1.3 mm).

¹H NMR (CDCl₃, TMS):

1.31-2.00 (m, 8 H, -CH₂-CH₂-CH₂-CH₂-),

2.05 (s, 3 H, OC-Me), 2.15 (s, 3 H, C=C-O-CO-Me),

2.15-2.69 (m, 6 H, ring H).

IR (neat, cm⁻¹): 1750 (enol ester C=O), 1705 (C=C).

MS, m/e (rel intensity): 254(M⁺; 0.1), 212(22),

170(19), 152(38), 134(7), 123(15), 111(10), 98(8),

97(100), 96(10), 95(11), 84(29), 83(7), 81(7), 79(11),

67(10), 43(27).

15. Preparation of 2-(5-acetoxypentyl)cyclopent-2-en-1-one [45]:

Following the general procedure of Bernady¹⁹⁷, to a 300 mL three necked round-bottomed flask fitted with a mechanical stirrer and a Dean Stark trap was added LiBr (15.5 g, 0.178 mol) and Li₂CO₃ (14.87 g, 0.20 mol) in 129 mL of DMF. The mixture was dried by continuous extraction overnight with 100 mL of benzene and finally benzene was removed. Meanwhile, to a well-stirred white suspension of CaCO₃ (8.76 g, 87.6 mmol) in 90 mL of CHCl₃ cooled to 0-5°C were added dropwise simultaneously at 0-3°C during 1 h, a solution of [44A] (20.4 g, 87 mmol) in 10.3 mL of CHCl₃ and a solution of Br₂ (14.02 g, 87 mmol) in 13 mL of CCl₄. The reaction mixture, which turned from

milky yellow to orange-yellow and then to milky orange, was stirred with cooling at the same temperature for 0.5 h, and the phases were separated. The aqueous phase was washed with CHCl_3 . The combined organic phases were washed with 5% NaHSO_3 , water and saturated NaCl solution, dried with Na_2SO_4 , and evaporated in vacuo at 40°C to yield 27.5 g of a bromoketone. This product was dissolved in 10 mL of dry DMF and then immediately added in one portion to the heated mixture of Li salts and DMF at 80°C dried as above. The beige-colored mixture, which was refluxed under N_2 for 0.5 h, became darker. The reaction mixture was cooled slowly, poured into 400 mL of ice-water, and acidified with concentrated HCl (about 34 mL) until the solid of the reaction mixture was dissolved and a brown tar was formed. It was extracted with 3 x 800 mL portions of ether, washed with 3 x 600 mL portions of water, then saturated NaCl solution (900 mL), dried with anhydrous Na_2SO_4 , and evaporated in vacuo. The residue was chromatographed on 600 g of silica gel, eluting with a gradient of 0 to 8% ethyl acetate-hexane (v/v) to yield 8.74 g (52%) of [45] as a colorless oil (lit¹⁹⁷ bp $116-118^\circ\text{C}/0.25\text{ mm}$).

^1H NMR (CDCl_3 , TMS):

0.87-1.78 (m, 6 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$),

2.04 (s, 3 H, CH_3-CO_2),

2.20-2.69 (m, 6 H, $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{C}-\text{CH}_2-$),

4.09 (m, 2 H, $-\text{CH}_2-\text{OCO}-\text{CH}_3$),

7.34 (m, 1 H, C=CH);

IR (neat, cm^{-1}): 1736 (ester C=O), 1700 (C=O),
1626 (C=C), 1238.

UV (max): 228 nm (ϵ 7800). MS, m/e (rel intensity):
210(M^+ , 2), 150(29), 135(21), 123(14), 122(82),
121(45), 117(13), 109(12), 108(34), 107(26), 97(12),
96(89), 95(46), 94(24), 93(23), 91(21), 81(19), 80(32),
79(95), 77(15), 68(10), 67(46), 66(17), 65(18), 55(33),
53(19), 43(100).

16. Attempt to prepare [45] from 1,2-bis(trimethyl-
siloxy)cyclopentene [45A]:

Part A: Preparation of [45A]:

Diethyl glutarate was submitted to the acyloin condensation using Me_3SiCl according to the modified procedure¹⁹⁸. The enediol-bis-trimethylsilyl ether [45A] was purified by distillation and obtained in 83% yield under a similar condition employed above (Na/Toluene/ Me_3SiCl), bp 115–117°C/20 mm (lit¹⁹⁸ bp 93–94°C/12 mm) as a colorless liquid.

Part B: Attempted alkylation of [45A]:

To a cold (–15 to –20°C) solution of [45A] in 25 mL of monoglyme was added dropwise 1.54 M MeLi in ether (14 mL, 22 mmol). The cloudy, white reaction mixture was stirred at –15 to –20°C for 30 min. After removal of the solvent under vacuum over 4 h at 30–70 mm, a mixed solvent of THF (7.5 mL) and HMPT (22.5 mL) was added to the red

brown residue continuously, and then [40A] (2.56 g, 10 mmol) was added dropwise over 25 min followed by stirring at -20°C for 1 h, then at 25°C for 2 h. The reaction mixture was diluted with brine containing 10% HCl (80 mL), extracted with 3 x 100 mL portions of ether, dried over anhydrous MgSO_4 , and concentrated to give an oily product which contained a mixture of 13 unidentified components and no 2-(5-acetoxypentyl)-2-hydroxycyclopentanone (desired product) was obtained (based on MS and ^1H -NMR analysis).

17. Conjugate addition of ethylmagnesium bromide to [45]:

To a stirred solution of 3 M EtMgBr in ether (3.5 mmol, 1.2 mL) at -7°C was added 1.67 mg of CuI. While maintaining the internal temperature of the dark brown reaction mixture between -7 and -5°C , a solution of [45] (0.48 g, 2.3 mmol) in 0.7 mL of anhydrous ether was added dropwise with rapid stirring. The reaction complex was decomposed by adding 0.7 mL of a cold saturated NH_4Cl solution, followed by dilute HCl (0.5 N), to give a clear solution. The ethereal layer was separated and the sky blue-colored aqueous phase was thoroughly extracted with six portions of ether. The combined extracts were dried with anhydrous MgSO_4 and concentrated on a rotary evaporator. The residue (0.4 g) was thin layer chromatographed on silica gel, eluting with 20% ethyl acetate-hexane (v/v) to yield 0.12 g (22%) of trans-3-ethyl-2-(5-acetoxypentyl)cy-

clopentanone [37], ($R_f = 0.27-0.22$), as a colorless oil. (See the results and discussion section for a discussion of the assignment of geometric isomers based on NMR.)

18. Conjugate addition of lithium diethylcuprate to [45]:

Ethyl bromide (0.4 g, 3.7 mmol) in 1.1 mL of anhydrous ether was added dropwise to Li wire containing 8% Na (0.67 g, 0.01 mol) in 3.7 mL of anhydrous ether under Ar with mechanical stirring at -20°C to give a cloudy, gray solution. After 1 h stirring at the same temperature, the solution of EtLi in ether was added slowly to a slurry of CuI (0.35 g, 1.8 mmol) in 1.8 mL of freshly distilled THF at -78°C . The resulting purple solution was stirred for 15 min and then a solution of [45] (0.38 g, 1.8 mmol) in 0.4 mL of freshly distilled THF was added at -78°C . Following a 10 min period at -78°C , Me_3SiCl (0.46 mL, 3.6 mmol) was added to the reaction mixture, and the cold bath was removed. On warming to room temperature (over ca. 1 h) the mixture was poured into a mixture of 50 mL of hexane, 0.28 mL of Et_3N and ice water. The cloudy, white hexane solution was separated from the yellow-green aqueous solution, and washed with NaHCO_3 solution to yield a sky blue-colored aqueous layer, which was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator to give 300 mg of the crude yellowish oily product. This product was thin-layer chromatographed on silica gel, eluting with 20% ethyl acetate - hexane (v/v) twice to give a colorless

oil [37] (cis/trans = 27/73, based on GC areas) (R_f = 0.35–0.42), yield 140 mg (32.5%).

19. Conjugate addition of lithium diethylcuprate to [45] in the presence of Me_3SiCl :

A solution of EtBr (3.19 g, 29.3 mmol) in 10 mL of anhydrous ether was added dropwise to a pea-sized piece of Li wire containing 0.8% Na (0.58 g, 83 mmol) in 34 mL of anhydrous ether at -10 to -20°C under Ar with mechanical stirring. After 2 h at -10 to -17°C the light gray, cloudy solution of EtLi was added to a white slurry of CuI (2.78 g, 14.6 mmol) in 16.7 mL of freshly distilled THF at -35 to -25°C over 11 min. The reaction mixture, which turned milky brightyellow, then burgundy red, and finally dark purple, was mechanically stirred under Ar at -35°C for 15 min and cooled to -78°C . A solution of Me_3SiCl (126 mL, 14.6 mmol) in 6.1 mL of freshly distilled THF was added dropwise to the solution at -78°C . This was immediately followed by the addition of a solution of [45] (2.56 g, 12.2 mmol) in 12 mL of dry THF over 3 min. On warming to room temperature for 1 h the reaction mixture, which turned dark red, then dark brown, was stirred for another 2 h. At this time the mixture was very dark purple, and it was added dropwise to a mixture of cold, vigorously stirred saturated NH_4Cl (400 mL) and ether (200 mL). The organic phase was separated. The sky blue-colored aqueous phase was extracted with 3 x 200 mL portions of ether. The combined ethereal extracts were

washed with 2 x 500 mL portions of saturated NaHCO_3 solution, dried with anhydrous Na_2SO_4 , and concentrated on the rotary evaporator to give 3.0 g of crude product [46].

^1H NMR (CDCl_3 , TMS): 0.16 (s, 9 H, SiMe_3),

0.90 (t, $J = 7.0$ Hz, 3 H, $-\text{CH}_2-\text{CH}_3$),

0.95-2.70 (m complex, 15 H),

2.04 (s, 3 H, $\text{OC}-\text{CH}_3$),

4.04 (t, $J = 6.7$ Hz, 2 H, $-\text{CH}_2-\text{O}-$).

IR (neat, cm^{-1}): 1750 ($\text{O}-\text{C}=\text{O}$), 1710 ($\text{C}=\text{C}-\text{OSiMe}_3$),

1690, 1640, 1260, 1240, 850, 760.

MS, m/e (rel intensity): 312(M^+ , 4),

283(15), 197(8), 152(7), 151(27), 133(17), 117(15),

109(19), 107(6), 105(8), 95(9), 93(23), 91(10),

81(11), 79(7), 75(28), 73(100), 55(9), 45(12),

43(80).

Without further purification [46] was converted to [37] by one of the following methods:

Method A:

The crude product [46] (0.15 g, 0.48 mmol) was thin-layer chromatographed on silica gel, eluting with 20% ethyl acetate-hexane to yield [37], which was identified by comparing MS, ^1H -NMR and R_f value with those of the authentic sample, 33 mg (29%) ($R_f = 0.35-0.42$). Cis/trans = 25/75 (based on GC areas).

Method B:

The impure [46] (0.14 g, 0.45 mmol) was stirred at room temperature for 24 h with a mixture of acetic acid

(45 drops), water (15 drops) and THF (15 drops). After removal of solvent in vacuum, the product was warmed in the flask with 0.02 mL of Et₃N at 130 °C for 1 h. Et₃N was removed to give 0.12 g of crude product [37], identified as above, which was then purified as in method A. Yield 20 mg (20%) from [46]. Cis/trans = 25/75 (based on GC areas).

Method C:

A solution of acetic acid (31.1 mL), water (10.4 mL), and THF (15.5 mL) was added to [46] (0.63 g, 2.0 mmol) (previously purified by column chromatography on silica gel, eluting with a gradient of 0-2% ethyl acetate-hexane) with stirring. The cloudy solution was allowed to stand at 50 °C for 4 h. The cooled reaction mixture was diluted with ethyl acetate and washed with 5% NaHCO₃ solution and water. The organic layer was dried over anhydrous Na₂SO₄. After removal of solvent, the crude yellow oil (0.48 g) was purified as in method A to give 0.24 g (50%) of [37] (colorless oily product). [37] was identified by comparing MS, GC retention time, ¹H-NMR, and R_f value with those of the authentic sample. The cis/trans ratio was 22/78 according to GC areas.

20. Reaction of trimethylsiloxycyclohexene [67] and aluminum hydride:

To a stirred solution of LiAlH_4 (1.1 g, 0.03 mol) in dry ether (44 mL) a light yellow solution of AlCl_3 (1.44 g, 0.01 mol) in 33 mL of dry ether was added. The reaction between LiAlH_4 and AlCl_3 was slightly exothermic (temperature increased from 25 to 28°C). The dark gray-colored mixture containing AlH_3 was left for 1 h at room temperature then [67] (1.8 g, 0.01 mol) (prepared as described in method 35) in dry ether (8 mL) was added dropwise. After 20-48 h of refluxing under N_2 or Ar the reaction mixture, which turned light gray, was cooled in an ice-bath and cautiously treated with ice cold aqueous acid (50 mL of 5 N HCl or 0.5 N HCl). (Note: a cold trap was attached to the end of the condenser). The ethereal layer was separated, and the aqueous layer extracted with 3 x 15 mL portions of ether. The combined ether layers were washed rapidly in succession with cold saturated NaHCO_3 solution (40 mL) and cold water (40 mL). The organic extracts were dried over anhydrous MgSO_4 . After the ether was removed, the extracts were carefully distilled to obtain fractions which contained cyclohexanone and cyclohexene, as shown by $^1\text{H-NMR}$, GC/MS and a qualitative test with Br_2/CCl_4 (Note: reaction of trimethylsiloxycyclohexene with Br_2/CCl_4 gives fumes and a cloudy solution; whereas

cyclohexene and Br_2/CCl_4 gives a colorless solution). In no case was the GC yield of cyclohexene greater than ca. 1%, so the method was not pursued further.

21. Preparation of 1-(5-acetoxypentyl)cyclopentene [48]
and 3-(5-acetoxypentyl)cyclopentene [47]:

To a rapidly stirred suspension of Zn dust (0.30 g, 4.7 mmol) in dry ether (6 mL) containing Me_3SiCl (0.26 g, 2.4 mmol) was added a solution of [43] (0.1 g, 0.47 mmol) in anhydrous ether (3 mL) to form a dark gray suspension. The reaction mixture, which turned slightly gray after 12 days stirring at room temperature, was filtered. The ethereal solution was washed with aqueous NaHCO_3 and water, dried over anhydrous MgSO_4 , and evaporated. The crude product was thin layer chromatographed on silica gel, eluting with 10% ether-hexane, to yield 6 mg (6.5%) of a colorless, oily product ($R_f = 0.36\text{--}0.46$) believed to be a mixture of [47] (ca. 10%) and [48] (ca. 90%). [43] was recovered in (65% yield).

^1H NMR (CDCl_3 , TMS):

[47]: 1.10–1.70 (m, 8 H, $[-\text{CH}_2-]_4$),

1.70–2.80 (m complex, 5 H, $-\text{CH}_2-\text{CH}_2-\text{CH}-$ ring),

2.05 (s, 3 H, $\text{O}=\text{C}-\text{Me}$),

4.04 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}-$),

5.69 (m, 2 H, $\text{HC}=\text{CH}$);

[48]: 1.10–1.70 (m, 6 H, $[-\text{CH}_2-]_3$),

1.70-2.80 (m, 8 H), 2.05 (s, 3 H, OC-Me),
 4.04 (t, $J = 7.0$ Hz, 2 H, -O-CH₂-),
 5.39 (m, 1 H, -C=CH-). IR (neat, cm⁻¹):
 for the mixture: 3050, 1745, 1590,
 1250. MS, m/e (rel intensity): [48] 196(M⁺, 3),
 136(37), 121(26), 108(33), 107(27), 96(22),
 95(70), 94(47), 93(92), 91(18), 82(38), 81(58),
 80(78), 79(100), 77(17), 69(18), 68(33), 67(99),
 66(20), 65(10), 61(14), 55(25), 54(11), 53(14),
 43(71), 41(33), 39(11); [47]: 196(M⁺, 4),
 136(18), 121(9), 108(10), 107(3), 95(12), 94(12),
 93(39), 80(46), 79(22), 67(100), 66(17), 61(14),
 43(22), 41(11).
 Anal. Calcd. for C₁₂H₂₀O₂: C, 73.47; H, 10.20;
 (See the results and discussion section for a discuss-
 ion at the structural assignments). Found: C, 73.60;
 H, 10.02.

22. Hydroboration of trimethylsilyl enol ethers of

[43]:

Part A: A solution of lithium diisopropylamide (LDA) was prepared in situ by addition of 2.6 M BuLi/hexane (0.70 mL, 1.5 mmol) to diisopropylamine (0.24 mL, 1.7 mmol) in dry THF (3.5 mL) at -78°C. The off-white solution was stirred at -78°C for 15 min. To the LDA solution [43] (50 mg, 0.23 mmol) in freshly distilled THF (0.05 mL)

was added dropwise under N_2 at $-78^{\circ}C$. The reaction mixture was stirred for a further 1 h, then Me_3SiCl (0.30 mL, 2.4 mmol) was added slowly to provide a white cloudy suspension. The mixture was allowed to warm to room temperature. After stirring for 1 h, solvent was evaporated in vacuo. Dry pentane (10 mL) was added and $LiCl$ was removed by gravity filtration in a glove bag. Evaporation of the filtrate in vacuo afforded silyl enol ether [50] (80 mg, off-white liquid) which was used for the next reaction without further purification.

1H NMR ($CDCl_3$, TMS): 0.21 (s, 9 H, $SiMe_3$),
1.20–2.50 (m, 13 H), 2.04 (s, 3 H, $OC-CH_3$),
4.05 (t, $J = 7.0$ Hz, 2 H, $-CH_2-O$),
4.57 (t, $J = 7.0$ Hz, 1 H, $-C=CH-$);

MS, m/e (rel intensity) [50]: 284(M^+ , 13), 183(7),
170(18), 169(100), 167(14), 157(12), 156(72),
155(54), 141(5), 117(28), 75(31), 74(7), 73(86),
43(12).

Part B: To an off-white solution of silyl enol ether [50] (62 mg, 0.22 mmol) in freshly distilled THF (0.011 mL) was added dropwise 1 M BH_3 .THF (1.1 mL, 1.1 mmol) at -5 to $0^{\circ}C$. Many bubbles were formed in the flask at the beginning, then a clear, colorless solution was obtained at the end of the addition. The cold bath was removed at once. The reaction mixture was warmed to room temperature and stirred for 1 h. A few drops of water (0.25 mL) were

added slowly to destroy any excess hydride. A cloudy solution was formed. This was followed by the addition of 12.5% HCl (0.164 mL) and reflux for 4 h. The aqueous layer was extracted with ether. The combined organic layer was washed with saturated NaHCO_3 , then with water, dried over anhydrous Na_2SO_4 and concentrated. The crude product (22.2 mg) was thin layer chromatographed on silica gel, eluting with 10% ether-hexane to afford 10 mg (33%) of a mixture of [47] and [52], ratio 40:60 (based on GC areas), $R_f = 0.10-0.24$, as colorless liquid. [47] was identified by comparison of ^1H NMR, IR and MS with that prepared in procedure 24. The minor components [47] had an MS identical to the minor component in procedure 21.

23. Preparation of 2-(5-hydroxypentyl)cyclopentanone

[53]:

A clear, yellow solution of [43] (1.26 g, 5.95 mmol) in 7% ethanolic KOH [prepared by dissolving 0.35 g (6.2 mmol) of KOH in 0.25 mL of water and diluting to 5 mL with ethanol] was kept at room temperature for 24 h. After the solvent in the cloudy, yellow solution was removed in vacuo, the residue was dissolved in water (1 mL) and extracted with 5 x 25 mL portions of ether to yield 0.74 g (74%) of [53] after ether removal.

^1H NMR (CDCl_3 , TMS): 0.90- 2.00 (m, 12 H),
2.00-2.50 (m, 3 H, $-\text{CH}_2-\text{CO}-\text{CH}-$),

3.64 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}-$);

IR (neat, cm^{-1}): 3400, 1740.

MS, m/e (rel intensity): 152($\text{M}^+-\text{H}_2\text{O}$, 1),

97(14), 95(2), 85(7), 84(100), 83(22), 67(10),

55(14), 54(6), 41(9), 39(5).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2$: C, 70.59; H, 10.59;

Found: C, 70.40; H, 10.65.

24. Hydroboration of 3-(5-trimethylsiloxypentyl)-2-trimethylsiloxycyclopentene:

Part A: Following procedure 22, [53] (0.16 g, 0.94 mmol) in dry THF (94 mL) was added to a solution of LDA [prepared in situ by addition of 2.6 M of BuLi in hexane (94 mL, 3 mmol) to diisopropylamine (0.347 g, 3.42 mmol) in dry THF (6.8 mL) at -45 to -60°C] under N_2 at -78°C over 2 min. The reaction mixture was stirred for a further 1 h, then Me_3SiCl (0.52 g, 4.8 mmol) was added. The mixture was worked up as described in procedure 22 to afford [54], 0.26 g (88.3%) as a yellow oil.

^1H NMR (CDCl_3 , TMS): 0.10 (s, 9 H, $-\text{C}-\text{O}-\text{SiMe}_3$),

0.20 (s, 9 H, $-\text{C}=\text{C}-\text{OSiMe}_3$),

1.20–2.50 (m, 13 H),

3.57 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}-$),

4.60 (m, 1 H, $-\text{C}=\text{CH}-$).

Part B: Following procedure 22, crude [54] (0.26 g, 0.83 mmol) in THF (0.32 mL) was treated with 1 M $\text{BH}_3\cdot\text{THF}$

(1.25 mL, 1.25 mmol), then with 10% HCl (1 mL), and refluxed for 4 h to provide crude [52] (0.1 g) which was thin layer chromatographed on silica gel, eluting with 20% ethyl acetate - hexane. Pure [52] was obtained as a colorless liquid 15 mg (11.7%) (R_f = 0.30-0.40). The product had identical NMR and MS properties to that prepared in procedure 22.

^1H NMR (CDCl_3 , TMS) [47]:

1.10-1.70 (m, 8 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$),
 1.70-2.80 (m complex, 5 H, $-\text{CH}_2-\text{CH}_2-\text{CH}-$),
 3.65 (t, J = 6.4 Hz, 2 H, $-\text{CH}_2-\text{O}-$),
 5.68 (s, 2 H, $-\text{CH}=\text{CH}-$).

IR (neat, cm^{-1}) [47]: 3400, 3060, 1620, 1260;

MS, m/e (rel intensity) [47]: 154(M^+ , 1), 136(10),
 121(6), 108(8), 107(7), 95(14), 94(12), 93(29),
 82(9), 81(9), 80(28), 79(17), 77(7), 68(10),
 67(100), 66(12), 65(8), 41(7).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 77.92; H, 11.69;

Found: C, 77.84; H, 11.80.

25. Preparation of 3-ethyl-2-(5-hydroxypentyl) cyclopentanone [55]:

Following procedure 23, [37] (0.49 g, 2.0 mmol) in 7% ethanolic KOH (2.1 mL) was kept at room temperature for 24 h. Working up the reaction mixture as usual, crude [55] (0.34 g, 86% yield) was obtained and used for the next re-

action without further purification.

^1H NMR (CDCl_3 , TMS):

0.95 (t, $J = 7.0$ Hz, 3 H, $\text{CH}_3\text{-CH}_2\text{-}$),

1.14-1.84 (m, 10 H),

2.06-2.70 (m, 6 H, $\text{-CH}_2\text{-CH}_2\text{-CO-CH-CH-}$),

3.63 (t, $J = 6.1$ Hz, 2 H, $\text{-CH}_2\text{-O-}$);

IR (neat, cm^{-1}): 3400, 1740;

MS, m/e (rel intensity): 180($\text{M}^+\text{-H}_2\text{O}$, 1), 125(7),

112(50), 97(7), 83(100), 67(10), 55(18), 41(11).

26. Hydroboration of the trimethylsilyl enol ether of

[55]:

Part A: Following procedure 22, crude [55] (0.32 g, 1.60 mmol) in dry THF (0.17 mL) was added to a solution of LDA [prepared in situ by addition of 2.6 M BuLi in hexane (1.45 mL, 3.28 mmol) to diisopropylamine (0.418 g, 4.13 mmol) in dry THF (8.3 mL)] under N_2 at -68 to -65°C . The reaction mixture was stirred for a further 1 h, then Me_3SiCl (0.70 mL, 5.53 mmol) was added. The mixture was worked up as in procedure 22 to yield [56] (0.54 g, 99%) as a yellow liquid.

^1H NMR (CDCl_3 , TMS):

0.11 (s, 9 H, -O-SiMe_3),

0.22 (s, 9 H, -C=C-OSiMe_3),

0.88 (t, $J = 6.5$ Hz, 3 H, $\text{-CH}_2\text{-CH}_3$),

1.10-2.80 (m, 14 H),

3.57 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}-$),

4.49 (t, $J = 2.0$ Hz, 1 H, $-\text{CH}=\text{C}-\text{O}-\text{SiMe}_3$);

MS, m/e (rel intensity): 342(M^+ , 4), 314(7),

313(24), 223(20), 196(6), 191(12), 183(11),

156(17), 155(71), 149(4), 147(12), 133(9), 103(5),

75(30), 74(9), 73(100), 55(5), 45(9).

Part B: Following procedure 22, crude [56] (0.54 g, 1.6 mmol) in dry THF (0.66 mL) was treated with 1 M $\text{BH}_3\cdot\text{THF}$ (2.51 mL, 2.51 mmol) then with 10% HCl (2.0 mL), and refluxed for 4 h to provide crude [57] (0.26 g), which was thin layer chromatographed on silica gel, eluting with 20% ether-hexane. Pure [57] was obtained as a colorless liquid, yield 0.19 g (65%), $R_f = 0.10-0.16$.

^1H NMR (CDCl_3 , TMS):

0.88 (t, $J = 7.0$ Hz, 3 H, CH_3-CH_2-),

1.07-1.70 (m, 10 H, $-\text{[CH}_2\text{]}_5-$),

1.71-2.62 (m, complex, 4 H, ring $-\text{CH}_2-\text{CH}-\text{CH}-$),

3.63 (t; $J = 6.4$ Hz, 2 H, $-\text{CH}_2-\text{O}-$),

5.68 (s, 2 H, $-\text{CH}=\text{CH}-$);

IR (neat, cm^{-1}): 3400, 3060, 1620,

1270; MS, m/e (rel intensity): 182(M^+ , 7), 135(21),

121(7), 109(8), 108(6), 107(6), 96(25), 95(100),

93(26), 81(15), 80(10), 79(34), 77(14), 67(45),

55(12), 41(7), 39(6).

Precise mass (by high-resolution mass spectrometry) for $\text{C}_{12}\text{H}_{22}\text{O}$, calcd. 182.1669, found: 182.1668.

27. Preparation of 4-ethyl-3-(5-acetoxypentyl)-
cyclopentene [20]:

A solution of [57] (51.1 mg, 0.28 mmol) and 0.1 mL of dry pyridine was prepared in a stoppered 5 mL round-bottomed flask, and 0.10 mL of acetic anhydride was added in four portions over a 15 min period. The mixture was stirred well for 12 min and allowed to stand for 6 h and then poured onto ice. Water was added (1 mL), and the mixture was extracted with 5 x 100 mL portions of petroleum ether (bp 35-60 C). The organic extracts were combined and washed in succession with 3 portions of saturated NaHCO₃ solution and with 3 portions of water. The organic layer was dried over anhydrous MgSO₄, then concentrated on a rotary evaporator to provide 62 mg (99%) of [20] as a colorless oil.

¹H NMR (CDCl₃, TMS):

0.89 (t, J = 7.0 Hz, 3 H, CH₃-CH₂-),

1.07-1.61 (m, 10H),

1.70-2.70 (m complex, 4 H ring),

2.04 (s, 3 H, OC-CH₃),

4.05 (t, J = 7.0 Hz, 2 H, -O-CH₂-),

5.69 (s, 2 H, -CH=CH-);

IR (neat, cm⁻¹): 3060, 2930, 2860, 1745, 1640,

1370, 1240, 1040. MS, m/e (rel intensity):

224(M⁺, 3), 136(15), 135(73), 121(19), 108(15),

107(17), 96(14), 95(100), 93(22), 91(11),
80(12), 79(37), 77(10), 67(37), 43(21), 41(7).

(See stereochemical assignment section for ^{13}C NMR data of [20].

Precise mass (by high-resolution mass spectrometry) for $\text{C}_{14}\text{H}_{24}\text{O}_2$, calcd. 224.1779, found: 224.1778.

28. Preparation of (5-acetoxypentyl)cyclopentane [59]:

A solution of the keto ester [43] (212 mg, 1.0 mmol) and *p*-toluenesulfonylhydrazine (0.24 g, 1.25 mmol) in a mixture of DMF-sulfolane (3.2 mL : 2.8 mL) containing 25 mg of *p*-toluenesulfonic acid was stirred at room temperature for 2.5 h. The light yellow solution was warmed up to 100 C, followed by addition of NaBH_3CN (0.2 g, 4 mmol), then 1.7 mL of dry cyclohexane and 2 mL of freshly distilled THF. The reaction mixture was heated at 105–110 C for 6 h, cooled to room temperature, diluted with 12 mL of water, and extracted 3 times with cyclohexane. The cyclohexane solution was washed twice with water, dried with anhydrous Na_2SO_4 , and concentrated on a rotary evaporator to yield a yellow oil, [59] (0.12 g). Crude [59] was purified by thin layer chromatography on silica gel, eluting with 10% ether-hexane, to give 20 mg (10.1%) of [18], $R_f = 0.32\text{--}0.47$.

^1H NMR (CDCl_3 , TMS):

1.00-1.76 (m, 17 H), 2.04 (s, 3 H, OC-CH₃),

4.05 (t, J = 7.0 Hz, 2 H, -CH₂-O-);

MS, m/e (rel intensity): 138(M⁺-AcOH, 10),

110(19), 109(17), 97(12), 96(81), 95(77), 83(27),

82(100), 81(57), 69(34), 68(60), 67(80), 66(11),

61(46), 55(39), 54(16), 43(51), 41(29).

¹³C-NMR: 171(O-C=O), 64.7(-CH₂-O-).

Precise mass (by high-resolution mass spectrometry) for C₁₂H₂₂O₂, Calcd. (M⁺-AcOH) 138.1408, found: 138.1405.

29. Preparation of 2-ethyl-1-(5-acetoxypentyl)

cyclopentane [18]:

Following procedure 28, [37] (42 mg, 0.17 mmol) was treated with p-toluenesulfonylhydrazine (50 mg, 0.27 mmol) in a mixture of DMF-sulfolane (0.44 mL: 0.44 mL) containing 4.4 mg of p-toluenesulfonic acid. After stirring at room temperature for 2 h then warming up to 100°C, NaCNBH₃ (35 mg, 0.55 mmol) then 0.3 mL of cyclohexane and finally 0.3 mL of DMF were added. The reaction mixture was worked up as in procedure 28 to give a crude product which was thin layer chromatographed on silica gel, eluting with 10% ether-hexane to afford [18] (4 mg, 10.4% yield) as colorless oil after evaporation of the solvent.

¹H NMR (CDCl₃, TMS):

0.95 (t, J = 7.0 Hz, 3 H, -CH₂-CH₃),

0.98-1.84 (m, 18 H), 2.04 (s, 3 H, OC-CH₃),

4.04 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}-$).

IR (neat, cm^{-1}): 1745, 1240;

MS, m/e (rel intensity): 166(M^+-AcOH , 8),
 155(6), 141(9), 139(6), 128(6), 137(24), 110(27),
 109(25), 98(9), 97(38), 96(100), 95(67), 94(10),
 91(10), 87(10), 83(14), 82(30), 81(87), 79(10),
 73(14), 70(15), 69(27), 68(23), 67(47), 66(9),
 65(10), 61(11), 57(10), 56(15), 55(63), 53(10),
 49(11), 45(9), 43(52), 41(20), 38(15).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_2$: C, 74.34; H, 11.50;

Found: C, 74.17; H, 11.45.

30. Preparation of 2-(5-acetoxypentyl)-4-carbethoxy-
 3-methyl-2-cyclohexen-1-one [61]:

A solution of Hagemann's ester^{195, 199} (936 g, 0.199 mol) in 200 mL of toluene containing 50% NaH dispersed in mineral oil (9.6 g, 0.20 mol) was mechanically stirred under N_2 at 110°C until no more hydrogen was evolved (ca. 1 h and 15 min). The reaction mixture turned light green-yellow, then yellow at room temperature, then tumeric-yellow as heated, and finally became red-orange. The cooled, very viscous reaction mixture was treated with 5-bromopentyl acetate [40] (41.6 g, 0.199 mol) and mechanically stirred under N_2 at reflux for 3 days. The ivory-colored mixture was cooled and stirred at room temperature for 4.4 h. Acetic acid (1.4 mL) was cautiously added

to decompose any excess NaH, followed by 200 mL of water. The toluene layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure to yield [61] 60.0 g (97.3%), which was used for the next reaction without further purification.

^1H NMR (CDCl_3 , TMS):

1.28 (t, $J = 7.0$ Hz, 3 H, $\text{CH}_3\text{-CH}_2\text{-C=O}$),
 1.41–1.90 (m, 8 H), 1.98 (s, 3 H, C=C-CH_3),
 2.05 (s, 3 H, OC-CH_3),
 2.20–2.50 (m, 4 H, $\text{OC-CH}_2\text{-CH}_2\text{-}$),
 3.25 (m, 1 H, $\text{-CH-CO}_2\text{Et}$),
 4.09 (t, $J = 7.0$ Hz, 2 H, $\text{-CH}_2\text{-OCO-CH}_3$),
 4.23 (m, 2 H, $\text{CH}_3\text{-CH}_2\text{-COO-}$).

IR (neat, cm^{-1}): 1735, 1725, 1665, 1635.

MS, m/e (rel intensity): 310(M^+ , 6), 250(8),
 178(8), 177(56), 176(17), 161(9), 159(16),
 150(12), 149(18), 148(9), 139(17), 135(41),
 134(8), 133(11), 123(45), 122(26), 121(100),
 111(11), 109(29), 108(11), 107(25), 105(11),
 91(24), 81(13), 79(31), 77(17), 69(14), 67(12),
 55(21), 43(41).

31. Preparation of 2-(5-acetoxypentyl)-3-methyl-2-cyclohexen-1-one [62]:

A mixture of [61] in 61.1 mL of acetic acid and

81.5 mL of 25% HCl was refluxed for 18 h. The reaction mixture changed gradually from a yellow, cloudy heterogeneous mixture to a brown, clear solution. After cooling, the solution was partitioned with 4 x 250 mL portions of benzene. The organic phase was washed with 5 x 45 mL portions of water until all traces of acid were gone, then with saturated NaCl solution (250 mL), dried over anhydrous Na_2SO_4 , and concentrated on a rotary evaporator. The resulting brown oil (42.3 g) was column chromatographed on silica gel, eluting with a gradient of 2–20% ethyl acetate–hexane, to give [62], 31 g (65.5%), $R_f = 0.19$ – 0.30 (26% petroleum ether–ether).

^1H NMR (CDCl_3 , TMS): 1.2–1.79 (m, 8 H), 1.93 (s, 3 H, $\text{C}=\text{C}-\text{Me}$), 2.04 (s, 3 H, $-\text{OC}-\text{CH}_3$), 2.28–2.8 (m, 6 H), 4.04 (t, $J = 7.0$ Hz, 2 H, $-\text{CH}_2-\text{O}$).

IR (neat, cm^{-1}): 1735 (ester $\text{C}=\text{O}$); 1655 (conjugated $\text{C}=\text{O}$), 1635 ($\text{C}=\text{C}$).

MS, m/e (rel intensity): 238 (M^+ , 24), 223(10), 196(10), 178(16), 163(31), 151(14), 150(26), 149(27), 137(20), 136(44), 135(59), 124(41), 123(37), 122(25), 121(13), 111(11), 109(12), 108(14), 107(23), 97(11), 96(60), 95(45), 94(16), 93(25), 91(27), 82(24), 81(33), 80(15), 79(65), 77(23), 68(12), 67(45), 65(28), 55(59), 53(20), 43(100), 41(44), 39(17).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_3$: C, 70.59; H, 9.24;

Found: C, 70.19; H, 9.36.

32. Hydrogenation of [62]:

A solution of keto ester [62] (1.1 g, 4.6 mmol) in 168 mL of 95% EtOH was shaken with 112.0 mg of 5% Pd on carbon in a Parr apparatus under initial hydrogen pressure of 50 psi. After 72 h, the mixture was filtered. The filtrate was dried over anhydrous Na_2SO_4 , and the solvent was removed under reduced pressure to provide 1.09 g (98.3%) of a colorless oil as a mixture 18:82 of cis:trans [63] (based on GC areas; see Result and discussion section for the stereochemical assignment).

^1H -NMR for the mixture (400 MHz, CDCl_3 , TMS): (major,

trans): 1.13 (d, $J = 6.6$ Hz, 3 H, $\text{CH}-\text{CH}_3$),

1.40–1.80 (m, 8 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$),

1.96–2.15 (m, 5 H, $-\text{CH}_2-\text{CH}_2-\text{CH}-$),

2.03 (s, 3 H, $\text{OC}-\text{CH}_3$),

2.35–2.47 (m, 3 H, $-\text{CH}_2-\text{CO}-\text{CH}-$),

4.04 (t, $J = 6.4$ Hz, 2 H, $-\text{CH}_2-\text{O}-$);

(minor, cis): 0.81 (d, $J = 7.0$ Hz, 3 H, $-\text{CH}-\text{CH}_3$),

1.12–1.40 (m, 8 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$),

1.80–1.95 (m, 5 H, $-\text{CH}_2-\text{CH}_2-\text{CH}-$),

2.03 (s, 3 H, $\text{OC}-\text{CH}_3$),

2.20–2.45 (m, 3 H, $-\text{CH}_2-\text{CO}-\text{CH}-$),

4.04 (t, $J = 6.4$ Hz, 2 H, $-\text{CH}_2-\text{O}-$).

^{13}C NMR data (see stereochemical assignment section).

IR (neat, cm^{-1}): 1750, 1720, 1250;

MS, m/e (rel intensity): (major, trans):

240(M^+ , 2), 113(5), 112(91), 98(9), 97(100), 95(7),
 81(6), 69(6), 67(6), 55(12), 53(20), 43(11), 41(6),;
 (minor, cis): 240(M^+ , 2), 113(4), 112(65), 98(5),
 97(100), 81(6), 69(30), 67(5), 55(10), 43(13), 41(4).
 Anal. Calcd. for $C_{14}H_{24}O_3$: C, 70.00; H, 10.00;
 Found: C, 70.10; H, 10.13.

33. Preparation of ethyl(or methyl) 1-(5-acetoxypentyl)
 -2-oxo-cyclohexanecarboxylate [64]:

To a stirred suspension of 50% NaH in mineral oil (29.3 g, 0.61 mol) in 338 mL of dry THF was added 100 g of commercially available 2-cyclohexanonecarboxylate (60% ethyl, 40% methyl esters) during 1.5 h while maintaining a temperature of 25°C. The green-yellow mixture was stirred for 15 min, warmed to 53°C, and treated with 5-bromopentyl acetate [40] (131.7 g, 0.63 mol) during 6 min. The dark yellow mixture was stirred at 59–63°C for 6.5 h under N_2 . The resulting ivory-colored mixture was cooled to room temperature with stirring for 3 h, poured into water (650 mL) and extracted with 3 x 400 mL portions of water until all traces of base were gone, then with saturated NaCl solution (400 mL). After drying over Na_2SO_4 the solvent was removed to afford a yellow oil with a fruity smell, [64] (169.8 g, 93% yield).

1H NMR ($CDCl_3$, TMS):

1.30 (t, $J = 7.0$ Hz, 3 H, $-CH_2-CH_3$ if $R = Et$),
 1.55–2.60 (m, 16 H, $-(CH_2)-$),

2.03 (s, 3 H, OC-CH₃),
 3.72 (s, 3 H, COO-CH₃ if R=Me),
 4.04 (t, J = 6.0 Hz, 2 H, -CH₂-O-CO-CH₃),
 4.24 (q, J = 7.0 Hz, 2 H, OC-O-CH₂-CH₃ if R=Et).

The mixture of esters was used without separation in the next reaction.

34. Preparation of 2-(5-acetoxypentyl)cyclohexanone

[66] from [64]:

A stirred mixture of crude [64] (170 g, 0.57 mol), 447 mL of glacial acetic acid, 94 mL of conc. H₂SO₄ and 445 mL of water was refluxed for 22.5 h. The cooled mixture was extracted with 3 x 400 mL portions of benzene. The organic layer was washed with 3 x 250 mL portions of water until all trace of acid was removed, then with 250 mL of brine and dried over anhydrous Na₂SO₄. The solvent was evaporated to afford a yellow oil (114.3 g, 83% crude yield from 2-cyclohexanonecarboxylate ester), which was chromatographed on silica gel, eluting with 2-10% ethyl acetate-hexane to give pure [66] (identified by comparison to the published spectra^{12a}, lit^{12a} bp 130-132°C/0.075 mm).

¹H-NMR (CDCl₃, TMS): 0.88-2.20 (m, 14 H),
 2.25-2.45 (m, 3 H, -CH₂-CO-CH-),
 2.04 (s, 3 H, -OC-CH₃),
 4.04 (t, J = 7.0 Hz, 2 H, -CH₂-O-),
 IR (neat, cm⁻¹): 1750, 1720, 1250;
 MS, m/e (rel intensity): 226(M⁺, 13), 111(7),

98(100), 95(4), 83(13), 70(8), 69(8), 55(11),
43(14), 41(6).

35. Preparation of [66] from cyclohexanone:

Following procedure 7, silyl enol ether [67] (8.5 g, 50 mmol), which was prepared from cyclohexanone by House's method²⁰⁰, was dissolved in dry THF (100 mL), and treated with a solution of lithium amide [prepared from Li wire (0.73 mg), 800 mL of ammonia, 300 mL of anhydrous THF and a trace of ferric nitrate] and then with a solution of 5-bromopentyl acetate [40] (41.8 g, 0.2 mol) in 50 mL of freshly distilled THF to give [66], yield 4.56 g (40.4%), bp 145-147°C/0.2 mm (lit¹⁷⁶ bp 130-132°C at 0.075 mm), identified by comparison of ¹H NMR and IR spectra with published spectra.

36. Preparation of 1-acetoxy-2-(5-acetoxypentyl) cyclohexene [68]:

Following procedure 14, keto ester [66] (111 g, 0.49 mol) was reacted with acetic anhydride (237 mL) and *p*-toluenesulfonic acid monohydrate (1.14g) to give crude [68] (95% pure based on GC), yield 128.6 g (98%).

¹H NMR (CDCl₃, TMS): 1.16-2.00 (m, 16 H),

2.05 (s, 3 H, -CH₃-O-CO-CH₃),

2.09 (s, 3 H, -C=C-O-CO-CH₃),

4.05 (t, J = 6.5 Hz, 2 H, -O-CH₂-);

IR (neat, cm⁻¹): 1755, 1738, 1705, 1220, 1030.

^{13}C NMR (CDCl_3): 20.76 (1C), 20.87, 22.43, 22.98, 25.72, 26.78, 27.03, 27.71, 28.39, 29.88, 64.44, 123.9, 142.2, 169.1, 171.

Anal. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_4$: C, 67.2; H, 8.96;

Found: C, 67.03; H, 9.11.

37. Preparation of 2-(5-acetoxypentyl)-2-cyclohexen-1-one [70]:

To a stirred solution of enol acetate [68] (10.9 g, 41 mmol) in 375 mL of glacial acetic acid and 62.5 mL of pyridine at 10°C was added a solution of Br_2 (6.9 g, 431 mmol) in 200 mL of glacial acetic acid during 20 min. The resulting solution was allowed to stand at room temperature for 45 min and then treated with NaHSO_3 . The solution was diluted with brine and extracted with 1:1 hexane: ether. The extract was washed with water and brine, dried over K_2CO_3 , and concentrated to give 13.2 g of crude bromoketone [69], which was used in the next step without purification.

^1H NMR (CDCl_3 , TMS): 1.45–3.0 (m, 16 H), 2.05 (s, 3 H, $-\text{OC}-\text{CH}_3$), 4.07 (t, $J = 6.2$ Hz, 2 H, $-\text{O}-\text{CH}_2-$).

A stirred suspension of LiBr (8.6 g, 99 mmol) and Li_2CO_3 (8.3 g, 112 mmol) in 100 mL of DMF was made anhydrous by boiling with benzene as described in the procedure 15. After benzene had been distilled, to the above mixture at 80°C was added a solution of the bromo-

ketone [69] in 25 mL of DMF in one portion. The stirred mixture was heated to reflux during 20 min and at reflux for 15 min, cooled, poured into 725 mL of 0.3 N HCl and extracted with ether. The extract was washed with water and brine, dried over anhydrous MgSO_4 , and concentrated. Column chromatography of the residue (9.16 g) on silica gel, eluting with a gradient of 0-10% ethyl acetate-hexane (v/v), gave [70] 5.7 g (62%).

^1H NMR (CDCl_3 , TMS):

1.14-1.97 (m, 8 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-$ of the ring),

2.04 (s, 3 H, $\text{O}=\text{C}-\text{Me}$),

2.05-2.30 (m, 4 H, 2 allylic $-\text{CH}_2-$),

2.43 (t, $J = 6.8$ Hz, 2 H, $-\text{CH}_2-\text{C}=\text{O}$),

4.04 (t, $J = 7.0$ Hz, 3 H, $-\text{CH}_2-\text{O}-$),

6.67 (m, 1 H, $-\text{CH}=\text{C}-$).

MS, m/e (rel intensity): 224(M^+ , 13), 182(9),

164(22), 149(22), 146(9), 137(14), 136(79),

135(63), 131(9), 123(20), 122(26), 121(26),

118(12), 117(11), 111(9), 110(16), 109(36),

108(45), 107(22), 105(10), 98(10), 97(10),

96(9), 95(33), 94(34), 93(46), 92(13), 91(27),

83(8), 82(45), 81(55), 80(50), 79(100), 77(34),

71(15), 68(9), 67(52), 66(18), 65(16), 55(69),

54(13), 53(41), 43(95), 41(41), 39(28).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_3$: C, 69.64; H, 8.93;

Found: C, 69.44; H, 9.00.

38. Preparation of silyl enol ether of [66]:

In a manner similar to part A of procedure 22, keto-ester [66] (598 mg, 2.64 mmol) in dry THF (1.5 mL) was added to a magnetically stirred solution of LDA [prepared in situ by addition of BuLi (1.2 mL of 2.6 molar solution in hexane (3.12 mmol) to diisopropylamine (0.5 mL, 3.56 mmol) in dry THF (6.4 mL)] under N₂ at -55°C. The reaction mixture, which became viscous, was stirred at -27 to -39°C. 3 mL of dry THF was added to make stirring easier. The suspension was magnetically stirred for a further 1 h. Me₃SiCl (0.6 mL, 4.74 mmol) was added dropwise over 30 sec. After working up as in procedure 22, a crude product (0.51 g) was obtained having 3 major components tentatively identified as: 22.3% of [71], 3.8% [72] and 35.6% of starting material [66] (based on GC and MS analyses).

¹H-NMR of the mixture (200 MHz, CDCl₃, TMS):

[71]: 0.19 (s, 9 H, -OSiMe₃),
 1.10-2.00 (m complex, 12 H),
 2.04 (s, 3 H, -OC-CH₃),
 2.10-2.50 (m, 2 H, -CH₂-C=C-),
 2.70-2.80 (m, 1 H, -CH-C=C-);
 4.04 (t; J = 7.0 Hz, 2 H, -O-CH₂-),
 4.80 (t, 1 H, -C=CH-).

[72]: 0.12 (s, 9 H, -OSiMe₃),
 1.10-1.80 (m complex, 14 H),
 2.20-2.70 (m, 3 H, -CH₂-CO-CH-),
 3.70 (t; J = 6.8 Hz, 2 H, -CH₂-O-),

4.40-4.60 (broad, 2 H, $-\text{CH}_2=\text{C}-$).

MS, m/e (rel intensity): ret time 10.4 min [71]:

298(M^+ , 8), 184(9), 183(61), 181(7), 171(12),
170(87), 169(28), 155(21), 142(10), 127(6),
117(18), 79(7), 75(38), 74(9), 73(100), 67(6),
55(7), 45(9), 43(20); [72] ret time 12 min:
298(M^+ , 2), 241(8), 201(33), 184(6), 183(8),
170(21), 149(6), 117(38), 115(63), 111(17), 99(11),
98(95), 97(16), 93(8), 83(17), 81(23), 79(11),
77(7), 76(6), 75(97), 74(12), 73(100), 72(9),
70(15), 69(56), 67(32), 55(57), 45(14), 43(20),
42(11), 41(42).

Because a mixture was obtained, this reaction was not investigated further.

39. Preparation of 2-(5-hydroxypentyl)-3-methyl- cyclohexanone [73]:

Following procedure 23, [63] (1.44 g, 6.0 mmol) in 7% ethanolic KOH (6.1 mL) was stirred at room temperature for 30 h. After working up the reaction mixture as usual, [73], 1.11 g (93%), cis:trans = 38:62 (based on GC areas), was obtained.

^1H NMR of the mixture (CDCl_3 , TMS):

0.85 (d, $J = 6.8$ Hz, 3 H, $-\text{CH}-\text{CH}_3$ cis),
1.07 (d, $J = 5.6$ Hz, 3 H, $-\text{CH}-\text{CH}_3$ trans),
1.10-2.70 (m complex, 16 H),
3.64 (t, $J = 6.10$ Hz, 2 H, $-\text{CH}_2-\text{O}-$);

IR (neat, cm^{-1}): 3400, 1710, 1105;

MS, m/e (rel intensity): (cis): 198(M^+ , 1),
112(48), 98(8), 97(100), 81(7), 67(9), 55(17),
41(7); (trans): 198(M^+ , 1), 112(45), 98(7), 97(100),
84(7), 81(6), 67(7), 55(14).

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_2$: C, 72.66; H, 11.20;

Found: C, 72.39; H, 11.42.

[73] was used for the next reaction without further purification. See the results and discussion section for a discussion of this structure assignment.

40. Hydroboration of the trimethylsilyl enol ether of [73]:

Part A: Following procedure 22, [73] (186.8 mg, 0.94 mmol) in dry THF (0.094 mL) was added to a solution of LDA [prepared in situ by addition of 2.6 M BuLi in hexane (0.82 mL, 2.13 mmol) to diisopropylamine (0.34 mL, 2.4 mmol) in dry THF (4.8 mL)] under N_2 at -78°C over 6 min. The reaction mixture was worked up as in part A of procedure 22 to provide silyl enol ether [74], yield 0.29 g (90.2%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3 , TMS):

0.11 (s, 9 H, $-\text{O-SiMe}_3$),

0.17 (s, 9 H, $-\text{C}=\text{C}-\text{O-SiMe}_3$),

0.90 (d, $J = 6.7$ Hz, 3 H, $-\text{CH-CH}_3$ trans),

0.94 (d, $J = 6.8$ Hz, 3 H, $-\text{CH-CH}_3$ cis),

1.20–2.50 (m complex, 14 H),

3.57 (t, $J = 6.7$ Hz, 2 H, $-\text{CH}_2-\text{O}-$),
 4.70 (m, 1 H, $-\text{CH}=\text{C}-\text{O}-$ cis),
 4.80 (m, 1 H, $-\text{CH}=\text{C}-\text{O}-$ trans);
 MS, m/e (rel intensity): (cis): 342(M^+ , 9.3),
 207(10), 197(35), 191(11), 184(36), 183(35),
 170(12), 169(77), 147(11), 95(11), 81(7), 79(8),
 77(8), 75(31), 73(100), 55(5), 45(8);
 (trans): 342(M^+ , 8.6), 184(29), 183(31), 170(11),
 169(78), 147(15), 95(10), 81(10), 75(29), 74(9),
 73(100), 55(5).

Part B: Following procedure 22, crude [74] (0.28 g, 0.83 mmol) in THF (0.33 mL) was treated with 1 M $\text{BH}_3\cdot\text{THF}$ (1.25 mL, 1.25 mmol) then with 10% HCl (1.0 mL) and refluxed for 4 h and 10 min to give crude [75], which was thin layer chromatographed on silica gel. Eluting with 10% ethyl ether-hexane, gave [75] cis:trans 47:53 (based on 400 MHz ^1H -NMR) as a colorless liquid, yield 95.8 mg (63.4%), $R_f = 0.07-0.02$.

^1H NMR 400 MHz (CDCl_3 , TMS):
 0.84 (d, $J = 7.1$ Hz, 3 H, $-\text{CH}-\text{CH}_3$ cis),
 0.95 (d, $J = 6.6$ Hz, 3 H, $-\text{CH}-\text{CH}_3$ trans),
 1.10-1.45 (m, 8 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ cis),
 1.45-1.75 (m, 8 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ trans),
 1.80-2.60 (m complex, 6 H, $-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}-$);
 3.64 (t, $J = 6.1$ Hz, 2 H, $-\text{CH}_2-\text{O}-$),
 5.63 (m, 2 H, $-\text{CH}=\text{CH}-$);

^{13}C NMR data (see stereochemical assignment section).

IR (neat, cm^{-1}): 3410, 3040, 1640, 1260;

MS, m/e (rel intensity): (cis): 182(M^+ , 5), 135(7), 110(12), 109(17), 108(9), 107(8), 96(34), 95(100), 93(26), 91(11), 82(13), 81(50), 80(15), 79(39), 77(14), 68(13), 67(44), 65(8), 55(24), 41(15); (trans): 182(M^+ , 7), 121(8), 110(14), 109(13), 108(10), 107(8), 96(29), 95(100), 93(19), 91(11), 82(13), 81(47), 80(12), 79(36), 77(11), 68(12), 67(47), 65(8), 55(18), 41(16), 39(7).

Precise mass (by high-resolution mass spectrometry) for $\text{C}_{12}\text{H}_{22}\text{O}$: Calcd. 182.1671; Found: 182.1671.

41. Preparation of 3-(5-acetoxypentyl)-4-methylcyclohexene [21]:

Following procedure 27, a solution of [75] (23.2 mg, 0.12 mmol) in 0.046 mL of dry pyridine was treated with 0.046 mL of acetic anhydride, and worked up as usual to yield [21], 17.8 mg, 80.4%, cis:trans 45:55 (based on GC areas) as a colorless oil. [21] was almost clean according to GC. No purification was attempted.

^1H NMR 400 MHz (CDCl_3 , TMS):

0.84 (d, $J = 7.2$ Hz, 3 H, $-\text{CH}-\text{CH}_3$ cis),
0.93 (d, $J = 6.8$ Hz, 3 H, $-\text{CH}-\text{CH}_3$ trans),
1.10-1.75 (m, 8 H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$),
1.80-2.55 (m, 6 H, $-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}-$),
2.05 (s, 3 H, $-\text{OC}-\text{CH}_3$),

4.04 (m, 2 H, -O-CH₂-),

5.61 (m, 2 H, -CH=CH-);

IR (neat, cm⁻¹): 3065, 1745, 1630,

1250, 1040; MS, m/e (rel intensity):

(cis): 224(M⁺, 4), 164(9), 149(19), 136(10),

135(22), 122(14), 121(22), 109(18), 108(33),

107(26), 96(26), 95(100), 94(25), 93(50), 91(17),

82(13), 81(46), 80(22), 79(52), 77(15), 68(12),

67(43), 65(7), 61(8), 55(22), 43(39), 41(9), 39(6);

(trans): 224(M⁺, 3), 164(13), 149(27), 136(9),

135(19), 123(70), 122(19), 121(26), 109(17),

108(28), 107(27), 97(7), 96(30), 95(100), 94(27),

93(63), 91(16), 82(13), 81(57), 80(26), 79(59),

77(19), 68(10), 67(64), 55(17), 43(43), 41(13), 39(9).

Precise mass (by high-resolution mass spectrometry) for C₁₄H₂₄O₂, Calcd. 224.1779; Found: 224.1778.

42. Preparation of 1-(5-acetoxypentyl)-2-methyl-cyclohexane [19]:

Following procedure 28, [63] (0.24 g, 1.0 mmol) was treated with p-toluenesulfonylhydrazine (0.24 g, 1.25 mmol) in a mixture of 1:1 DMF-sulfolane (2.5 mL:2.5 mL) containing 25 mg of p-toluenesulfonic acid. After stirring the mixture at room temperature for 2.5 h, warming up to 108°C, NaBH₃CN (0.2 g, 4 mmol) was added in 2 portions over a 1 h interval. DMF (3.5 mL) was used to rinse NaBH₃CN down to the reaction flask. Then 1.7 mL of dry cyclohexane was add-

ed. The cloudy, off-white solution was heated to reflux at 82-90°C for 8.5 h and worked up as in procedure 28. Crude product (0.24 g) was thin layer chromatographed on silica gel, eluting with 10% ethyl ether-hexane to afford [19] cis:trans = 39:61 (based on 400 MHz ¹H-NMR), R_f = 0.27-0.29, 38.5 mg (17%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃, TMS):

0.82 (cis) (d, J = 7.1 Hz, 3 H, -CH-CH₃),

0.88 (trans) (d, J = 6.5 Hz, 3 H, -CH-CH₃),

0.92-1.91 (m complex, 18 H),

2.05 (s, 3 H, -OC-CH₃),

4.05 (t, J = 6.6 Hz, 2 H, -O-CH₂-);

¹³C NMR data (see stereochemical assignment section).

IR (neat, cm⁻¹): 1745, 1240;

MS, m/e (rel intensity): (cis): 166(M⁺-AcOH, 13),

110(18), 109(23), 98(7), 97(73), 96(100),

95(61), 83(11), 82(30), 81(44), 79(7), 69(24),

69(16), 67(34), 61(28), 56(8), 53(6), 43(35),

42(6), 41(21), 39(6); (trans): 166(M⁺-AcOH, 12),

110(12), 109(19), 98(8), 97(93), 96(100), 95(50),

83(10), 82(26), 81(43), 79(7), 70(6), 69(24),

68(18), 61(33), 55(97), 43(34).

Anal. for C₁₂H₂₆O₂: C, 74.34; H, 11.50;

Found: C, 74.34; H, 11.65.

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VITA

Danh Thi Vu Nguyen was born in Saigon, South Vietnam. After graduation from Gia Long High School, she entered the University of Saigon, where she studied natural science and biochemistry. After the Saigon government fell in April, 1975, she emigrated to the United States. In August, 1975, she enrolled at New England College in Henniker, New Hampshire, where she studied chemistry under the direction of Dr. John J. Santos. After graduation from N.E.C in August, 1978, she married her classmate, Binh Thanh Nguyen, then they entered together the Graduate School at Pennsylvania State University, Department of Chemistry and worked under the direction of Prof. Maurice Shamma. In August, 1980, she and her husband entered the Graduate School of Louisiana State University in Baton Rouge, where she is, at present, a candidate for the degree of Doctor of Philosophy in chemistry. She performed her research under the direction of Prof. Frank K. Cartledge.

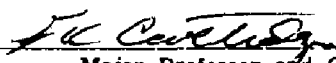
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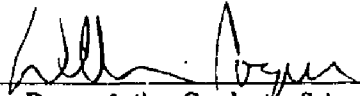
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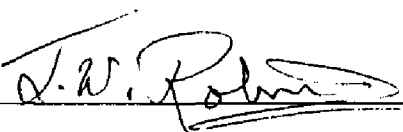

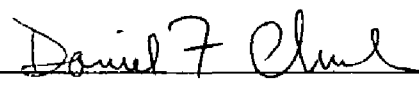

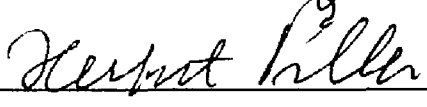
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